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HUMAN EVOKED POTENTIALS

Applications and Problems

Edited by
Dietrich Lehmann
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HUMAN EVOKED POTENTIALS

Applications and Problems

Edited by Dietrich Lehmann
University Hospital, Zurich, Switzerland

and Enoch Callaway
University of California, San Francisco

Human Evoked Potentials presents a multidisciplinary selection of recent papers discussing such topics as event related potentials in development, aging and dementia, color evoked potentials, and spatial and temporal distribution of olfactory evoked potentials and their measurement. Also examined are the uses of evoked potentials in the diagnosis of neuropathology, adaptation effects, and ERP scalp topography, as well as other physiological and psychological topics of interest.

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PREFACE

From August 25 - 28, 1978 a conference on averaged evoked potentials was held at Konstanz, West Germany. Research on human evoked potentials has progressed rapidly in the past decade, and a series of international conferences have served to maintain communication between active workers in the field. Among the organizations that have a tradition of supporting such multi-national communication are the North Atlantic Treaty Organization Scientific Affairs Division, the U.S. Office of Naval Research and the German Research Society (Deutsche Forschungsgemeinschaft). We have been fortunate to have the support of all three.

In the early stages of planning, a committee was formed composed of Professors Rudolph Cohen (Konstanz), Otto Creutzfeldt (Goettingen), John Desmedt (Brussels), A.M. Halliday (London), Anthony Remond (Paris) and Herbert Vaughan (New York). A call for papers was circulated as widely as possible, and this committee carried out the difficult task of selecting a limited number of participants from a large number of excellent abstracts.

At the same time Professor Cohen of the University of Konstanz was generous enough to shoulder the task of playing host to the conference. His thoughtful arrangements contributed enormously to the comfort of the participants. He and his colleagues also engineered an ideal ambience for sharing of ideas and observations, while the University of Konstanz generously provided audio-visual support.

Finally, it would be entirely appropriate for Danielle Thouvenin to be one of the senior authors on this volume, for she not only supervised the organization of the conference but edited and retyped all the manuscripts.

This volume represents an attempt to make available the results of a conference on ongoing research. Speed of publication has been our primary goal, and we have forgone some editorial niceties so these papers can be made available to other working groups while they are still current. The topic is an interdisciplinary one, and

papers could have been classified a number of ways (methods, disciplines, major focuses, etc.). We have, however, arranged them by senior author in alphabetical order.

Poster sessions played a large role in the sharing of new ideas and data, and the abstracts of these poster presentations are also in this volume. Active participation of all who attended was perhaps the most crucial factor in the conference, and the editors wish to thank them for their enthusiasm and their efforts. The final preparation of this volume has depended on the cooperation of Plenum Press and the technical assistance of Dr. Charles Yingling.

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AUDITORY, SOMATOSENSORY AND VISUAL EVOKED POTENTIALS IN THE
DIAGNOSIS OF NEUROPATHOLOGY: RECORDING CONSIDERATIONS AND
NORMATIVE DATA

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Recent advances have led to an increased ability to use initial components of the human auditory (AEP) and visual (VEP) evoked potential as a neurophysiological probe for the detection of CNS disorders (for reviews see e.g., Starr et al., 1978; Halliday, 1978). These advances were quickly followed by a successful search for subcortical portions of the somatosensory evoked potential (SEP) which could be applied similarly to neurological problems (Matthews et al., 1974; Cracco and Cracco, 1976; Jones, 1977; Hume and Cant, 1978). For purposes of differential diagnosis and better localization of lesions it will often be desirable to record EPs to the three modalities of stimulation. A few studies have already appeared using combinations of EPs (e.g., Mastaglia et al., 1976; Stockard and Sharbrough, 1978). The need thus arises for a review of the problems involved in combining AEP, SEP and VEP recording in a test which can be carried out in a single recording session. This paper will consider recording conditions and available normative data in such a clinical context. In referring to electrode location the subscripts *c* and *i* will denote locations contralateral and ipsilateral to the side of stimulation. All components are labelled by their polarity and approximate peak latency; AEP components P2-P9 correspond to waves I-VII as usually described.

Interest in subcortical AEP components is intense, and they have been applied to various diagnostic problems. Component amplitudes vary considerably in the normal population and are not generally useful. Peak latencies in studies reporting quantitative data are summarized in Figs. 1 and 2 and lead to these conclusions: (1) Most of the normative data reported to date are for young children or young adults. (2) On the right of Figs. 1 and 2, peak

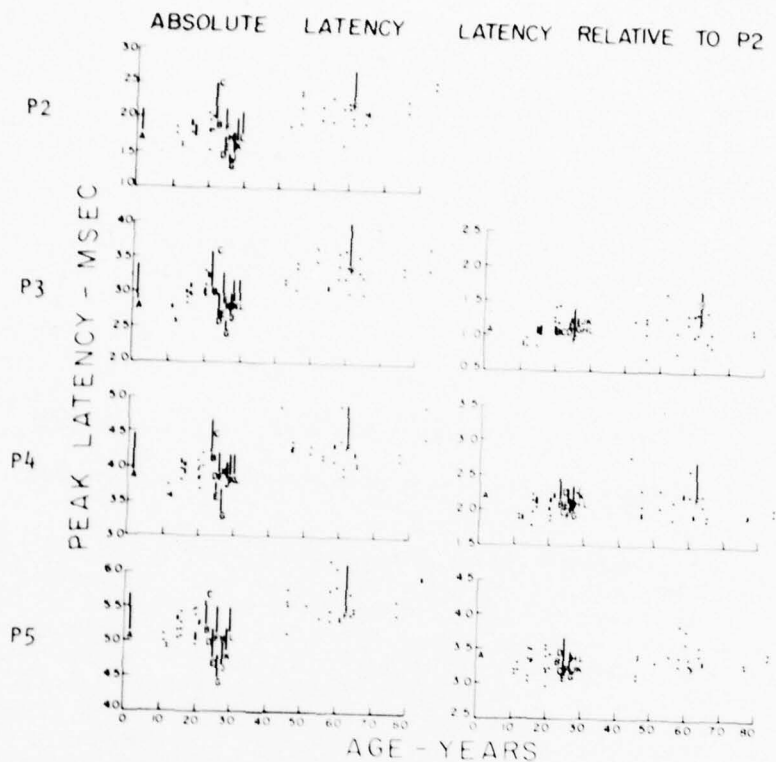


Fig. 1. Age related changes in AEP peak latencies and latencies relative to P2. Mean latency (letter) and +2 SD (vertical line) as determined by: A, Salamy and McKean, 1976; B, Stockard and Rossiter, 1977; C, Goff et al., 1978; D, Picton et al., 1974; E, Gilroy and Lynn, 1978; F, Rowe, 1978; G, Gilroy et al., 1977; H, Don et al., 1976; J, Starr and Achor, 1975 (75dB HL); K, Starr and Achor (65 dB HL); L, Picton et al., 1977. Dots are preliminary data of present study.

latencies are given relative to P2 which reflects the eighth nerve volley. Use of the peripheral nerve benchmark against which later components are measured provides a considerable reduction in between-laboratory variability, primarily because the effects of varying stimulus intensities used by different workers are partialled out due to parallel latency-intensity functions (e.g., Starr and Achor, 1975; Huang and Buchwald, 1978). (3) Fewer data are available for P7 and P9 which may reflect activity at the level of the medial geniculate nucleus and thalamocortical radiations, respectively (Stockard and

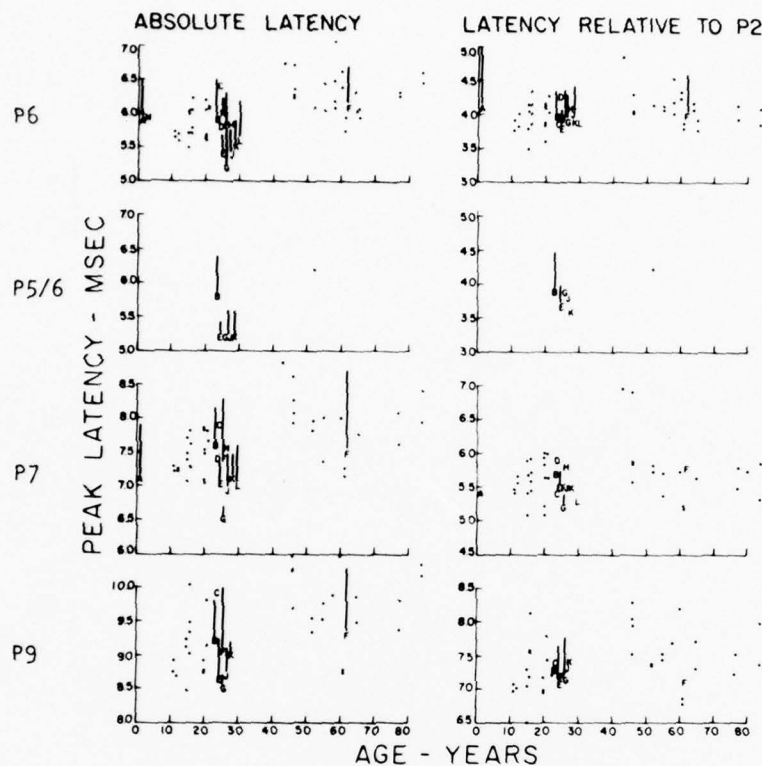


Fig. 2. AEP component latencies. Details as in Fig. 1.

Rossiter, 1977). P9 is often followed by a small deflection, P12, of unknown origin; no previous data are available. While P7, P9 and P12 are more variable in latency and appearance than are the earlier components, they are usually reproducible in a given subject. The preliminary data summarized in Figs. 1 and 2 suggest that absolute latencies increase with age but that latencies relative to P2 are fairly constant.

Recording electrode locations are reasonably consistent in previous work. Activity is typically recorded between Cz and an electrode on the mastoid or earlobe ipsilateral to the ear stimulated. Considerable variation exists in other recording parameters. The following are representative and were used for the preliminary data summarized in Figs 1 and 2: N = 1024 (2048 if necessary); filters at 30-3000 Hz (-3 dB points); intensity, 75 dB SL; stimulus rate, 10 sec; recording from Cz-Ai.

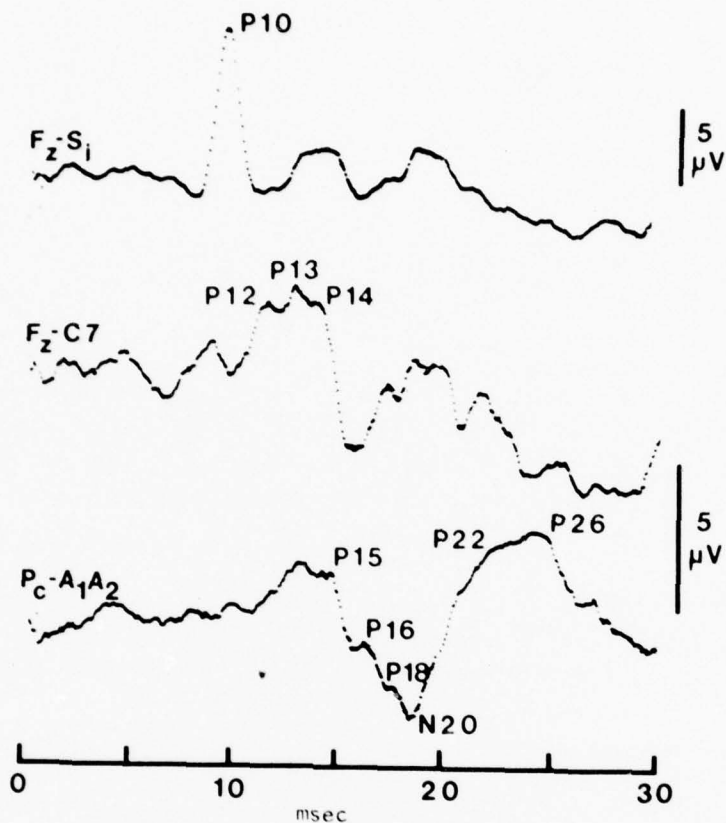


Fig. 3. Early SEP components recorded from derivations shown; details in text.

Although short latency SEPs of subcortical origin have been recorded for years (for a review see Allison et al., 1978), detailed recording of such activity using high resolution techniques is recent. No consensus has been reached as to optimal recording conditions, nor is it clear that all workers are observing exactly the same activity. By analogy with the subcortical AEP, it should be possible to use the subcortical SEP in evaluation of brain stem and midbrain pathology; promising preliminary results have been reported (Mastaglia et al., 1976; Greenberg et al., 1977; Hume and Cant, 1978; Stockard and Sharbrough, 1978).

We will first describe these components obtained from our standard recording conditions, then discuss the rationale for these conditions. The potentials are illustrated in Fig. 3 and are derived from a combination of the techniques described by Matthews et al., Cracco and Cracco, Jones and Hume and Cant. Following the convention used for the subcortical AEP, positive at scalp leads (Fz or Pc) is recorded upward. The top trace is the median nerve compound action potential recorded at the level of the shoulder ipsilateral (Si) to the stimulated median nerve. The middle trace illustrates later subcortical potentials P12, P13 and P14. The lower trace shows the subcortical potential P15 and the earliest cortical potential N20.

By analogy with the AEP, it should be useful to record a peripheral nerve benchmark with which later components can be compared. As would be expected there is a high correlation (about .80) between the latency of these components and body height or arm length (Matthews et al.; Hume and Cant; Dorfman 1977). Use of a peripheral nerve benchmark removes most of this source of variability in adults. Peripheral nerve conduction velocity varies with temperature (e.g., Buchthal and Rosenfalck, 1966). For clinical purposes it is not feasible to regulate arm temperature; use of the benchmark should remove this source of variability. Cracco and Cracco recorded the peripheral nerve volley at the level of the brachial plexus from Erb's Point, while Jones recorded it from the clavicle. In most subjects either of these locations yields a large, easily quantified potential. In normal subjects we found that a location midway along the clavicle yielded a potential about one-third larger (and earlier by 0.3-0.4 msec) than that recorded from Erb's Point. Since P10 is small in some older subjects and patients, the mid-clavicular placement seems preferable.

Components P12, P13 and P14 can be recorded either from scalp electrodes to a noncephalic reference (Cracco and Cracco), from electrodes over the cervical spine to a noncephalic reference (Jones) or from a cervical spine-midfrontal scalp derivation (Matthews et al.; Jones; Hume and Cant). In the scalp-noncephalic derivation these components are recorded as positive potentials, whereas in cervical spine-noncephalic recordings they appear as negativities (Fig. 4A). The origin of these potentials is not considered here (see Jones; Hume and Cant; Goff et al., 1978), but it will be useful to determine why they are recorded "locally" as negativities and rostrally as positivities. Cracco (1973) and Allison et al., (1978) interpreted an N14 potential (an amalgam of the P12, P13 and P14 components as recorded here) as reflecting the cervical cord afferent volley. If this interpretation is correct for P12, P13 and P14, a "killed-end equivalent" recording would satisfactorily account for the fact that these potentials are recorded from the scalp as positivities (Fig. 4B). On the other hand, some of these

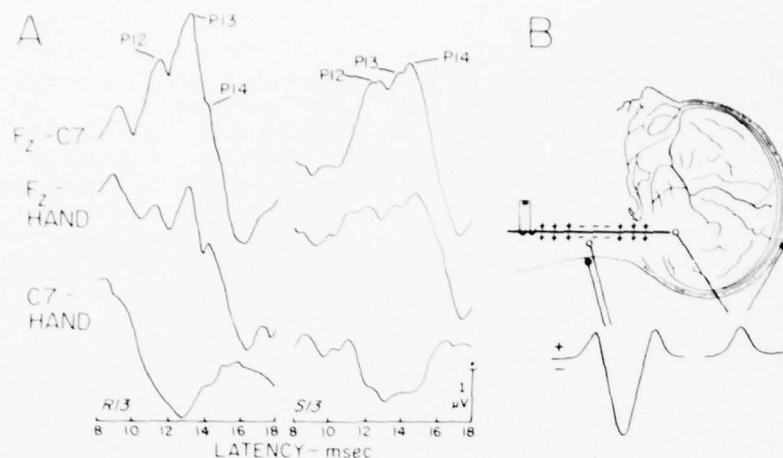


Fig. 4. Field potential properties of SEP P12, P13 and P14. A. P12, P13 and P14 are recorded as positivities in the Fz-hand derivation and as negativities in the C7-hand derivation; the Fz-C7 derivation yields their sum. B. Possible model to explain the results of A. Assume an isolated nerve preparation with recording (open circles) and stimulating electrodes as shown. An electrode on the nerve will record a negativity (sink) when the region of depolarization passes under the electrode and positive (source) potentials just before and after. An electrode at or beyond the end of the nerve will record a monophasic positive source potential ("killed-end effect"; e.g., Landau, 1967). Now imagine this nerve to be a fiber tract (e.g., dorsal column or medial lemniscus). As recorded from surface electrodes (closed circles) its compound action potential will be recorded as a negativity from the neck and as a positivity from the scalp.

components are thought to reflect activity generated in fixed sites (Matthews et al.; Jones; Hume and Cant); in this case it may be assumed that local sources mainly lie rostral to the depolarizing sinks and form a dipole field oriented in the rostral-caudal plane. Whatever the origin of these potentials, operationally the Fz-C7 derivation introduced by Matthews et al. takes advantage of their dipolar properties (cf. Jones) and yields an optimal recording. Noncephalic reference derivations are more subject to stimulus, EKG and muscle artifact and yield components of variable waveform. P12 and P13 are robust potentials, measurable in almost all normal subjects. P14 sometimes appears as a distinct peak (e.g., Fig. 3) but more often appears as a shoulder or inflection on the falling phase of P13. When P14 is difficult to measure in the Fz-C7 derivation

it can sometimes be seen better in the Pc-ALA2 derivation (Matthews et al., Fig. 1). As noted by Jones, P12 and P13 sometimes break up into subpeaks which can make determination of latency difficult.

In the Pc-ALA2 derivation, P13 and P14 are followed by P15 (Fig. 3). P15 can be the largest in this sequence of potentials, or it can appear only as a shoulder. It should be noted that the P15 potential recorded in earlier work (e.g., Allison et al., 1978) is an amalgam of the P13, P14 and P15 potentials as recorded here. N20 is generally regarded as reflecting initial activity of somatosensory cortex. It is large and easily measured in normal subjects. As noted by Cracco and Cracco, one or two positive deflections are often seen between P15 and N20; in Fig. 3 they are tentatively labelled P16 and P18. When only one deflection is apparent its categorization may be difficult. As noted by Hume and Cant, the waveform following N20 is variable in morphology. In some cases there is a single positivity at about 25 msec, but two peaks at about 22 and 26 msec are often seen. These are tentatively labelled P22 and P26 in Fig. 3 although in this example they are not clearly distinct. It is likely that P22 and P26 as measured here correspond to P25 and P30 as recorded by "standard" methods (e.g., Goff et al., 1977), the difference being due primarily to differing preamplifier high frequency bandpass.

Hume and Cant studied amplitude and latency of some of these potentials as a function of stimulus intensity. They found virtually no change in latency from an intensity just above sensory threshold to the maximal level tolerated. Amplitude increased only slightly from an intensity just below thumb twitch to the maximal level tolerated. Thus an intensity near thumb twitch threshold appears to be a good compromise between response amplitude and subject comfort.

Most studies not dealing specifically with the lower extremities have used median nerve stimulation at the wrist as a stimulus because it is convenient, because it evokes a large SEP and because the thumb twitch so produced provides an objective measure of stimulus intensity. It has been argued, however, that stimulation of a mixed nerve has the disadvantage of evoking an antidromic volley in motor fibers which might confound the recording of sensory afferent activity (Desmedt, 1971). While this argument has merit, the following considerations weigh against the use of finger stimulation: (1) Jones compared early SEP components to wrist and finger stimulation and found that all components were smaller but identifiable to finger stimulation. He concluded that none of the early SEP components can be wholly due to antidromic conduction in motor fibers since such fibers are not present at the base of the fingers and stimulation of the fingers was not seen to produce a direct motor response. We have also investigated this question and reach the

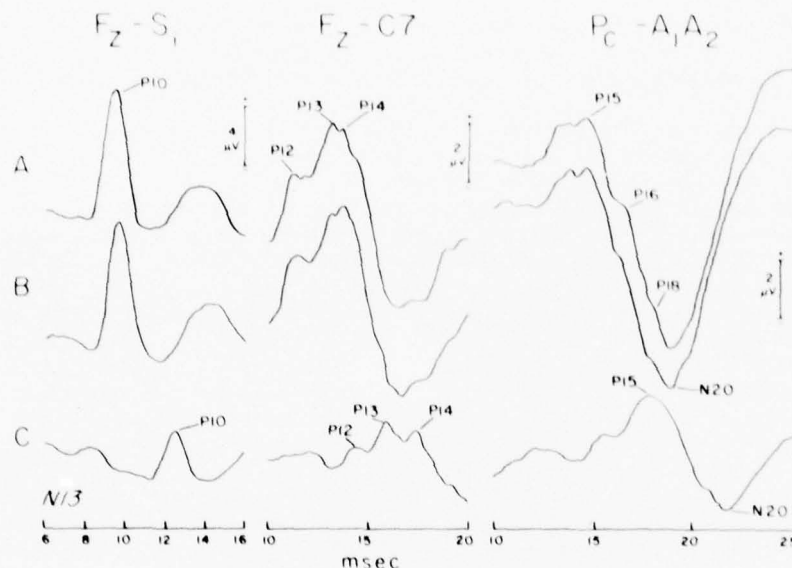


Fig. 5. Early SEP to stimulation of median nerve at an intensity just suprathreshold for thumb twitch (A), below thumb twitch threshold (B) and to stimulation of first and second fingers (C). Note similarity of waveforms in middle and top rows and presence of all components (except P16?) to finger stimulation.

same conclusion (Fig. 5). Note that all components are present at a stimulus intensity below thumb twitch threshold and to stimulation of the second and third fingers at an intensity subjectively equal to that evoking a thumb twitch. (2) Most patients are apprehensive about being "shocked", and subjective estimates of stimulus intensity to finger stimulation will often be unreliable. The small size of the peripheral nerve volley recorded from S_1 to finger stimulation (Fig. 5) renders it unsatisfactory as an index of stimulus efficacy. (3) Dawson (1956) first showed, and later studies (e.g., Rosner and Goff, 1967; Hume and Cant) have amply confirmed, that SEP components are near their maximum amplitude at threshold for a motor response. (4) Comparative studies have concluded that SEP waveform to tactile stimuli is similar to (although smaller and later than) the response evoked by median nerve stimulation (e.g., Nakamishi et al., 1973). These facts argue that little or none of the SEP is attributable to stimulation of motor nerve fibers. In our opinion the known advantages of using median nerve stimuli outweigh the potential disadvantages which remain to be demonstrated.

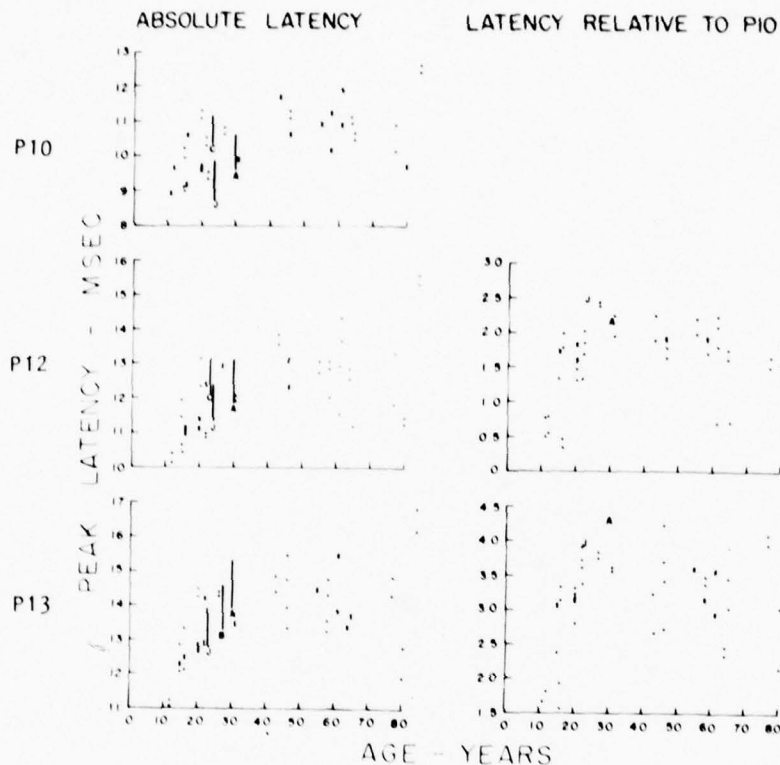


Fig. 6. Age related changes in SEP latencies in this and previous studies: A, Hume and Cant, 1978; B, Matthews et al., 1974; C, Cracco and Cracco, 1976; D, Nakanishi et al., 1973; E, Levy et al., 1971; F, Goff et al., 1977; G, Luders, 1970; H, Laquet et al., 1976; J, Jones, 1977; L, Dorfman and Bosley, 1978; M, Aleeve and Varezkhin, 1976. Details as in Fig. 1. Discrepancies in P10 and P10-relative latencies result from fact that P10 latency is earlier in the Fz-C7 derivation used by Jones and Hume and Cant than in the Fz-Si derivation (Fig. 3).

Stimulus frequencies of 1-10/sec have been used to record these potentials. In a pilot study we stimulated at 5 and 10/sec; waveforms and latencies were similar in both cases. In addition to requiring less recording time, the use of 10/sec stimuli might have the advantage of providing more of a neurophysiological "challenge", thus revealing abnormalities not detectable at lower rates of stimulation (Hecox et al., 1977). However, stimuli evoking a thumb twitch can be unpleasant at this rate; hence we have adopted 5/sec as a standard rate.

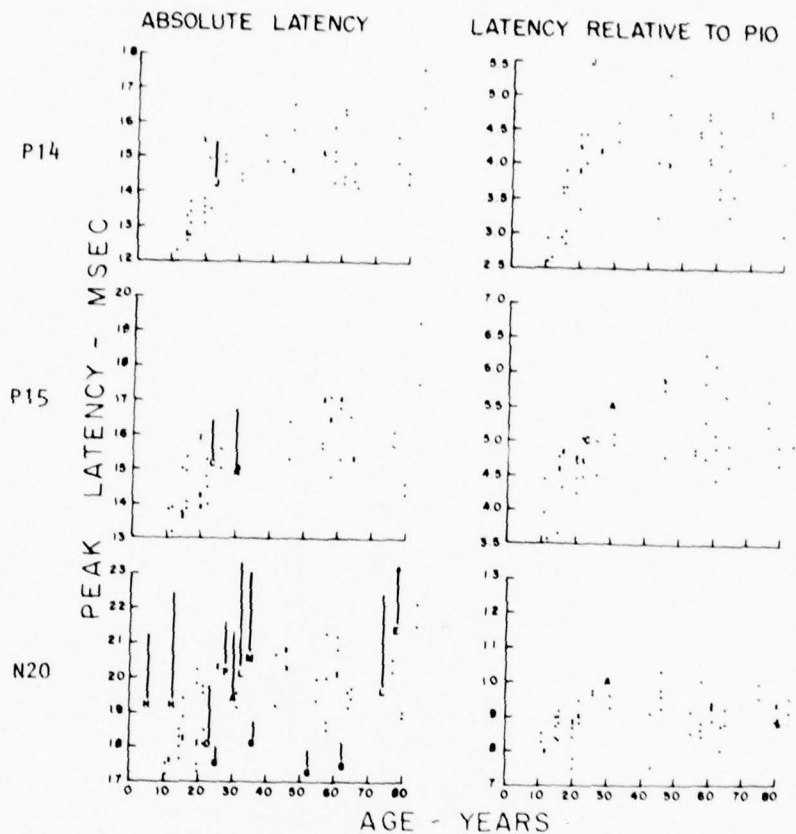


Fig. 7. Age related SEP latency changes. Details as in Figs. 1 and 6.

Components P15, N20, P22 and P26 are best recorded from the scalp to an ear reference. Some workers have recorded N20 from a Cc lead. However, this potential inverts in polarity across the central sulcus and hence is small in amplitude and variable in waveform at Cc (Goff et al., 1977). We record P15 and later components from a Pc-ALA2 derivation.

These considerations led to adoption of the following parameters: $N = 512$; filters at 30-3000 Hz (-3dB points); median nerve stimulus which just produces a thumb twitch; stimulus rate, 5/sec; three recording channels as in Fig. 3. Preliminary data using

these conditions are summarized in Figs. 6 and 7. It appears that both absolute latencies and latencies relative to P10 will show significant age related trends. Use of these potentials in the assessment of neuropathology has hardly begun (but see Mastaglia et al., 1976; Small et al., 1977; Hume and Cant; Stockard and Sharbrough, 1978), and it is too early to say which will be useful. Of the subcortical components, P14, P16 and P18 may prove less useful than the others because of difficulty of measurement. P22 and P26 may reflect cortical activity occurring later than that generating N20 and may not yield additional information.

The P100 component of the pattern reversal VEP has proved useful in detection of optic nerve pathology of varying etiology (Halliday, 1978). A drawback of this test is that P100 latency varies as a function of several stimulus parameters, primarily luminance and pattern reversal time. Analogous to the subcortical AEP, a peripheral benchmark component which would partial out these effects would be useful in allowing between-laboratory use of normative data, a hazardous procedure at present (Fig. 8A). Since the optic nerve is itself the primary source of abnormality (assuming no retinal pathology), the ERG provides the only possible benchmark. The b-wave of the ERG has been recorded to pattern reversal stimuli using a contact lens (Armington et al., 1971) but this method is not feasible for routine use. Halliday et al. (1973) recorded a small ERG to pattern reversal stimuli using a canthus-infraorbital derivation. In a number of normal subjects and patients we have attempted to record the ERG from various locations near the eye but with little success. We agree with Halliday (personal communication) that in this recording situation the ERG is too low in amplitude and broad in waveform to be useful. Unfortunately, this means that each laboratory must construct its own normative standards or adhere very closely to the stimulating and recording conditions of a laboratory reporting such data.

It is clear that P100 latency can increase in older persons (e.g., Asselman et al., 1975; Hennerici et al., 1977), but the form of the age-latency function is not clear. The data of Keltner et al. (in prep.) (Fig. 8B) suggest a gradual decline in latency to about age 50 with a progressive increase thereafter, whereas Celestia (in Starr et al., 1978) reports a progressive increase in latency with age. Preliminary results of the present study (Fig. 8B) do not resolve the question. The difference may be more apparent than real and reflect the small sample sizes and their age distribution. The present data were obtained using the following conditions which are representative of those employed in previous work: N = 128 (256 if necessary); filters at 1-300 Hz (-3dB points); intensity 1760 cd/m² (light squares), 35 cd/m² (dark squares); squares subtend a visual angle of 50'; entire pattern subtends 16°; reversal rate, 2/sec; electrode locations, O1 and O2 referenced to Fz. Halliday

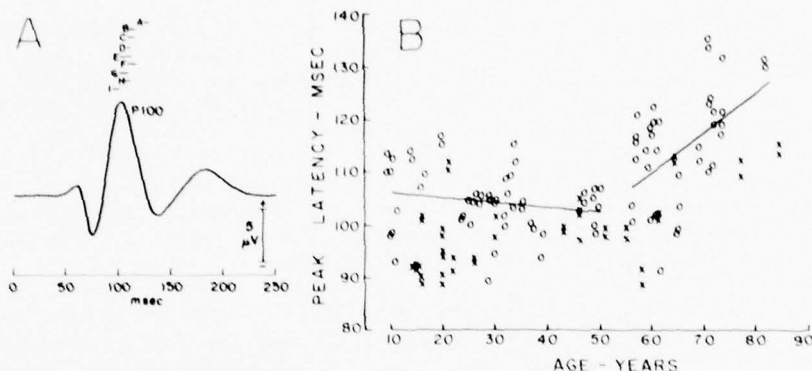


Fig. 8. A. Mean (letter) ± 2 SD (horizontal line) of VEP P100 peak latency as determined by: A, Halliday et al., 1973; B, Halliday (in Goff et al., 1978); C, Shahrokhi et al., 1978; D, Zeese, 1977; E, Celestia (in Starr et al., 1978); F, Keltner et al., in prep.; G, preliminary results of present study; H, Hennerici et al., 1977; I, Asselman et al., 1975. B. Age related changes in VEP P100. Circles: data of Keltner et al., in prep. Regression lines for 10-50 and 50-80 age groups shown. Crosses: preliminary results of present study. Latency differences in the two studies are due mainly to differences in checkerboard luminance and rapidity of pattern reversal.

prefers locations slightly rostral and lateral to O1 and O2; we find that Halliday's placements yield a P100 whose latency is equal to or earlier than that recorded from O1 and O2 but whose amplitude is usually smaller.

Using the recording conditions described above, three replications to stimulation of each ear, median nerve and eye can be obtained in approximately two hours including hook-up time. It is, therefore, feasible to obtain a fairly comprehensive assessment of the functional integrity of afferent sensory pathways up to or including sensory cortex. However, proper interpretation of such recordings will require adequate age-related normative data which the present preliminary results suggest will be complex.

SUMMARY

The early subcortical portion of the auditory and somatosensory evoked potentials and the P100 component of the pattern reversal visual evoked potential are increasingly used in neurological assessment. Review of the current state of such recordings suggests these

conclusions: 1. Recording of subcortical SEP components with high resolution techniques is recent; no consensus has emerged regarding optimal recording conditions or component origins. 2. Adequate age-related normative data for peak latencies are not available for any modality. This problem is compounded by the sensitivity of latency to stimulus parameters and recording conditions. 3. In the AEP and SEP, latency variability can be reduced by using the peripheral nerve volley as a "benchmark". 4. Preliminary results suggest that age-related latency changes are complex and must be taken into account in assessing neurological dysfunction.

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ADAPTATION EFFECTS IN THE TRANSIENT VISUAL EVOKED POTENTIAL

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INTRODUCTION

Implicit in the measurement of the averaged transient visual evoked potential (VEP) is the assumption that the visual system returns to a state of rest between stimuli. A signal enhancement technique such as averaging should display the signal which is the technique itself. Hence the temporal characteristics (stimulus duration and presentation rate) of the stimulus regime should be such that the above assumption is valid, or the averaging procedure may itself alter that which it seeks to measure. A lower limit to the rate of stimulation is effectively set by the stationarity of the background EEG (Cohen and Sances, 1977), and by the difficulty of maintaining a constant psychological state over periods of more than a few seconds. The upper limit is set by the transition to a steady state VEP, when the individual components become indistinguishable. Between these limits there is considerable scope for variation. The aim of this study is to investigate the dependence of the averaged transient VEP upon temporal stimulus parameters, with particular reference to the effects of adaptation upon the components of the pattern VEP.

Pattern adaptation was demonstrated by Gilinsky (1968) who showed that pre-exposure to a patterned light flash raised the psychological threshold for perception of a visual display of the same pattern form (but not others). That the VEP could be affected was shown by Blakemore and Campbell (1969) who used prestimulus adaptation to a pattern to produce a general reduction in the amplitude of the VEP, the amount of reduction depending upon the length of time for which the adapting pattern was presented. James and Jef-

Jeffreys (1975) investigated the effect of pattern pre-exposure on the components of the pattern onset VEP and commented that these effects could be observed in a conventional averaging run unless the stimulus duration is a small fraction of the interstimulus interval. Subsequently Jeffreys (1977) showed how variations in stimulus duration and interstimulus interval could affect the VEP waveform, and MacKay (1977) demonstrated that adaptation effects could be observed even if the pre-exposed pattern was formed by contrasting textures. Long stimulus sequences might be expected to accentuate any adaptation effects, and a number of authors have reported results of such statistics.

METHODS

Four subjects between 26 and 43 years of age participated in these experiments, three males and one female, two right-handed and two left-handed. All had normal visual acuities and visual fields and all were experienced observers.

The visual stimulus is a television based system, similar in many respects to that described by Arden et al. (1977). Two differences are worthy of note. The pattern generator has crystal-controlled synchronization giving a frame rate slightly different from the mains and thus permitting frame-locked stimulus presentation without mains-locked artifacts. Secondly, it is used with a projection television (Advent Videobeam). In this study a black and white checkerboard pattern was used throughout with check sizes subtending either 15', 30' or 60' of arc at the subject. The screen itself subtended angles of 26° (horizontal) and 20° (vertical). A fixation spot produced by slightly incrementing the pattern luminance at the appropriate point was positioned at the screen center. The luminance of the bright squares was 10 cd m⁻² and that of the dark squares 3.1 cd m⁻². For pattern onset VEPs the background (i.e., interstimulus) luminance was adjusted so that the integrated illuminance remained constant for both pattern and blank display. For flashed pattern VEPs the screen was dark (0.1 cd m⁻²) between stimulus presentations. For pattern reversal VEPs the luminance values of adjacent checks were interchanged at the stimulus frequency.

A silver/silver chloride electrode was used, positioned 2.5 cm above theinion on the midline and referenced to a similar electrode placed midfrontally (as Michael and Halliday, 1971). Earlobes were grounded. The bandwidth of the (Medelec Van Gogh) amplifier was 0.1 - 35 Hz, and the signals were averaged on a Nicolet MED-80 minicomputer using a simple amplitude criterion for artifact rejection. Raw data was also recorded on magnetic tape.

For experiments involving variation of either stimulus duration or interstimulus interval an average of 64 VEPs was taken. The various different values of independent variable were presented to the subject over a number of sessions in a balanced square design as appropriate. The procedure was replicated for each stimulus mode and, where used, for each different check size. For experiments involving long term adaptation a run of 600 stimulus presentations was used; each presentation mode and, where applicable, check size was presented to each subject on three separate occasions. Subjects were seated in a dimly illuminated room (illuminance at the subject equal to the stimulus illuminance used) and allowed to adapt to this level for a period of ten minutes in order for the effect of dark adaptation upon the VEP to become stable (Klingaman, 1976). Subjects were instructed to count the number of stimulus presentations in an attempt to maintain a constant level of attention. Binocular stimulation was used throughout.

RESULTS

For pattern onset and flashed pattern VEPs three peaks are always clearly visible: a positive peak at 100-120 msec latency, a negative peak at 130-150 msec and a second positive peak at 200-220 msec. They are taken to be components I, II and III as described by Jeffreys (1972), Lesevre and Remond (1972) and Spekreijse et al. (1973). Differences in latency are assumed to be due to differences in luminance and contrast of the patterns used by different authors. It is expected that the latencies in this study will be relatively long since, although a high contrast pattern is used, the luminance is relatively low. For pattern reversal responses a single positive peak at approximately 100 msec latency is predominant, although in some subjects negative peaks on either side of it, and even a second positive peak at around 200 msec latency are seen with varying degrees of clarity. The 100 msec peak, as described by Halliday and Michael (1970) is used as the measure in this study. If it is assumed that these components may represent distinct cortical processes, then it is essential to measure their amplitudes independently; peak-to-peak measures will always confound the properties of two components. It is thus necessary to define a suitable baseline, and in this work it was taken to be the mean value of VEP recorded in the first 40 msec after stimulus presentation. The notations CI, CII and CIII will be used hereafter to apply to the positive 100-120 msec, negative 130-150 msec and positive 200-220 msec peaks, respectively, as measured from this baseline. P100 will be used for the predominant peak in the reversal VEPs.

Experiment (i)

The effect of different stimulus duration upon component

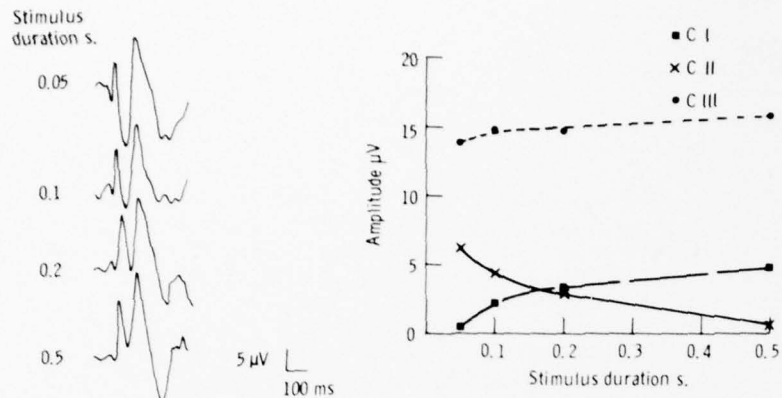


Fig. 1. The effect of stimulus duration. The left half-figure shows (single subject) flashed pattern VEPs for stimulus durations of 50, 100, 200 and 500 msec with a constant interstimulus interval of 500 msec. Positivity is up. The right half-figure shows component amplitude as a function of duration (mean across subjects and sessions). 15' checks were used.

amplitudes was investigated for a fixed interstimulus interval of 500 msec using flashed pattern presentation of a 15' check.

The VEPs obtained (Fig. 1) show an increase in the amplitude of CI and a clear decrease in the amplitude of CII, with increasing stimulus duration; changes in CIII are less marked. A description of the behavior of CI is possible using the concept of "residual contrast" which is present at stimulus onset due to the incomplete disappearance of contrast representation from the previous stimulus presentation. Such a mechanism was proposed by Spekreijse et al. (1973). They also demonstrated that the VEP to an increase in standing contrast may be treated as a pattern onset VEP with its starting point part way up the amplitude vs contrast curve, providing the standing contrast does not produce appreciable adaptation. Since the component amplitude reaches zero whilst there is still some contrast present, it is possible for a small standing contrast to produce an increase in amplitude. Hence it could be postulated that for CI there is a small residual contrast, the magnitude of which increases with stimulus duration but remains sub-threshold under the conditions of the experiment. The behavior of CII is indicative of adaptation with an integrative adaptation process. Although the data are few, regression analysis provides a good fit to an exponential relationship (correlation coefficient > 0.99) with an adaptation time constant of approximately 200 msec. CIII shows an insignificant amplitude increase with duration

increase, which could be interpreted as evidence of adaptation obviating the residual contrast.

Experiment (ii)

An alternative way of examining the same effects is to keep the stimulus duration constant and vary the interstimulus interval. In the first instance this was carried out using a flashed pattern stimulus of 200 msec duration with intervals from 0.3 sec to 4.0 sec. The duration of 200 msec was chosen so that the pattern offset response, which was clear in some subjects (but absent in others), was sufficiently delayed with respect to the components being measured, so as not to interfere with them. Check sizes of 15', 30' and 60' of arc were used.

Examination of the VEPs (Fig. 2) shows a clear and steady increase in CII with increase in interstimulus interval. The changes in both of the positive components are less marked. The relationship between check size and component amplitude is as previously described (Barber and Galloway, 1976), with CI maximized for large checks and CIII for small; this relationship holds over the whole range of intervals tested. For each component at each check size the graph has a bifid form, suggesting the involvement of more than one process. For CI and CIII the bifid nature is much more apparent for the larger checks. The initial peaks in the curves for CI may be explained by means of the residual contrast model used previously. If the responses to medium rate stimulation are unsaturated, the effect of high values of residual contrast will be to cause saturation and decrease the VEP amplitude; this condition will apply for very short interstimulus intervals. As the interval is increased the amount of residual contrast will decrease, and a point will be reached where it becomes subthreshold. This corresponds to the initial maximum on the curve. Thereafter, as the residual contrast becomes further subthreshold, the component amplitude will decrease until it reaches a steady value at the interval for which no residual contrast remains. The shape of the curve for intervals in excess of this value is not in good agreement with the model; one possible source of error may be the presence of luminance related effects due to the flashed pattern presentation. The more marked effect for larger checks for both CI and CIII is in agreement with the findings of Kulikowski (1977), who has shown that the contrast threshold is higher for patterns of low spatial frequency. The curves for CIII are similar in form to those of CI, and the initial part, at least, could be explained in terms of residual contrast attenuated by adaptation. The apparent shift of the first peak towards a shorter value of interstimulus interval would be in agreement with this, as would the more pronounced slope for the larger checks. The minimal net effect for the small checks might account for the insignificant variation in CIII in the previous

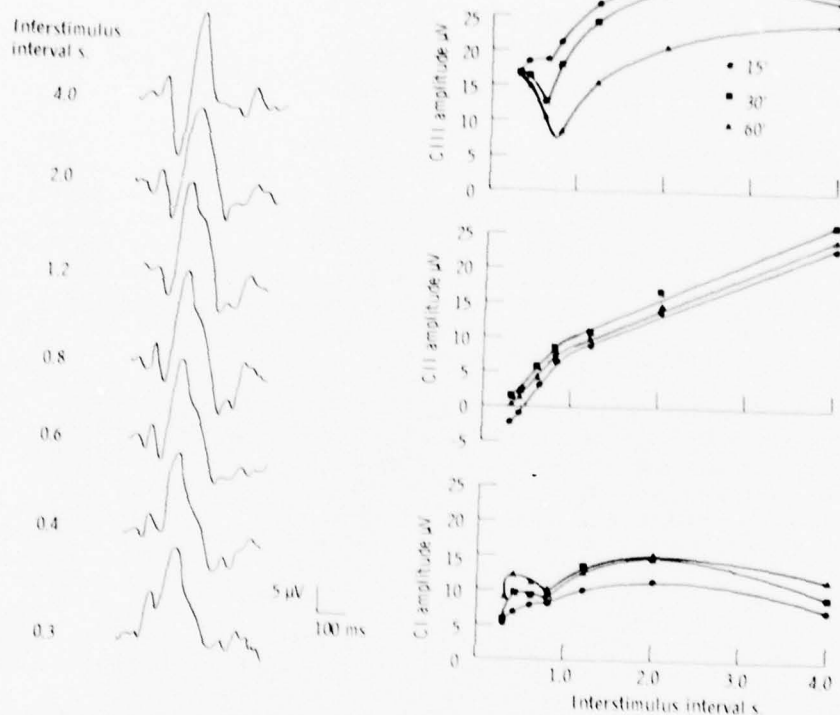


Fig. 2. The effect of interstimulus interval. The left half-figure shows (single subject) VEPs to a flashed pattern of 15' checks. Interstimulus intervals from 0.3 to 4.0 sec are used with a constant duration of 200 msec. Positivity is up. The monotonic increase in CII is clearly seen. The right half-figure shows component amplitude as a function of interstimulus interval for check sizes of 15', 30' and 60'.

experiment. The duplex linear curves obtained for CII are unusual, but regression analysis shows a much better fit (correlation coefficient > 0.99 for all subjects and all check sizes) than for the exponential function which might be expected. Having adapted during the stimulus presentation, CII appears to undergo linear recovery, with accelerated recovery in the residual contrast period. The parallel curves indicate that the effect is independent of check size. Again, the involvement of luminance effects is a possibility.

The experiment was repeated for pure pattern onset responses and the opportunity taken to increase the range of interstimulus

intervals in order to try to determine the interval at which CII levels off. The stimulus duration was increased to 500 msec so that the response recorded was pure pattern onset. In other respects the procedure was identical to that used for the previous part of this experiment except that only one check size (30') was used.

The results (Fig. 3) show that for CI there is definitely a luminance contribution. With this removed, the residual adaptation model describes the curve well. For short interstimulus intervals it also describes the curve for CIII, but for the longer intervals the amplitude of this component begins to decrease. Examination of our VEPs suggests that CIII may be composed of two peaks which are not resolved at normal intervals, but which are visible for a very long interval. Hence the peak normally measured may be a summation of two peaks. The length of time for which residual contrast persists shows an increase compared with the flashed pattern curves. This is due to the increase in stimulus duration from 200 msec to 500 msec, and the size of increase is in good agreement with the 200 msec adaptation time constant derived earlier. The curve for CII is unchanged; furthermore, the rate of increase in amplitude is unchanged, even for intervals as long as 9 msec.

In all the work described thus far, stimulus presentation has been regular, and there remains the possibility that this regularity itself influences the VEP. The experiment was, therefore, repeated using a series of random interstimulus intervals, each with a mean value equal to one of the values of intervals used previously and a range of $\pm 50\%$ of this value. The results show a similar relationship for the positive component as has been obtained previously. For CII, however, whilst there is still a clear increase in amplitude with interval, the bifid form obtained for regular presentation is not discernable. Clearly, regularity has an effect, though it

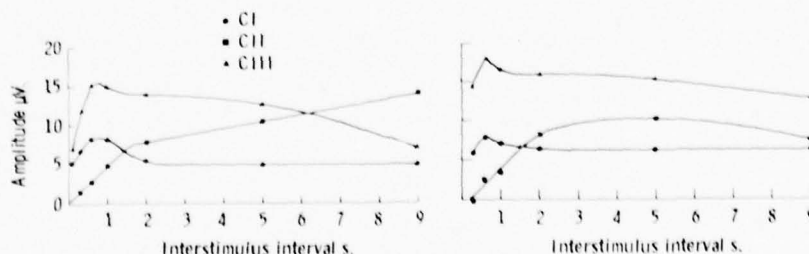


Fig. 3. Component amplitude as a function of interstimulus interval for pattern onset VEPs (mean across subjects and session). The left hand graph refers to a regular stimulus sequence. The curves for CI and CIII are modified compared with those for flashed pattern VEPs, but that for CII is unchanged. The use of an "interval indicator" (right hand graph) modifies the behavior of CII for long interstimulus intervals.

is not clear whether this is due to physiological or psychological factors; controlling temporal uncertainty by means of an "interval indicator" modifies the latter part of the CII curve but nothing else.

The basic experiment was also carried out using regular stimulus periods for pattern reversal responses. In this case the P100 component was measured, being the only component recognizable in all cases. The largest response was obtained from a subject from whom we have consistently been unable to obtain an offset VEP. This suggests that reversal VEPs, obtained by a television stimulus, may be similar to those described by Jeffreys (1977) for tachistoscope presentation as opposed to those obtained by pattern movement. The dependence of P100 on interstimulus interval was slight and varied from subject to subject. In some there was a slight increase in amplitude with increase in period; in others a slight decrease. Overall, no adaptation effects were observed for reversal VEPs. It is not possible to tell from this experiment whether pattern reversal fails to stimulate those components which are subject to adaptation or whether the constant presence of the pattern simply adapts them out.

Experiment (iii)

Whereas the previous experiments have been concerned with processes occurring with individual stimulus presentations and interstimulus intervals, the final experiment is aimed at demonstrating the effects of these processes as observed over large numbers of stimulus presentations. There are two reasons for doing this. One is that any small effects may thereby become more apparent. The other is to test the predictions of the model derived for the adaptation and recovery of CII. A system with exponential adaptation and linear recovery characteristics gives a value for the amplitude of the VEP to the n th stimulus which converges quite rapidly to a steady value as n increases from zero and thus predicts a rapid decrease in amplitude followed by a constant amplitude VEP. The actual rate of convergence in any given set of conditions will depend upon the values of the parameters used; with values obtained in this study a steady value is predicted after approximately five stimuli. Long sequence experiments were carried out on each subject using flashed pattern, pattern onset and pattern reversal stimulus modes. In the case of flashed pattern, small (15') and large (60') checks were used. For pattern onset and pattern reversal, medium (30') checks were used. The VEPs were evaluated simply by averaging contiguous blocks and producing plots of amplitude vs block number. In the first instance 32 VEPs were averaged per block.

The results for each of the different components and stimulus presentation modes are shown in Fig. 4, except that the graphs for pattern onset and flashed pattern presentation are very similar and

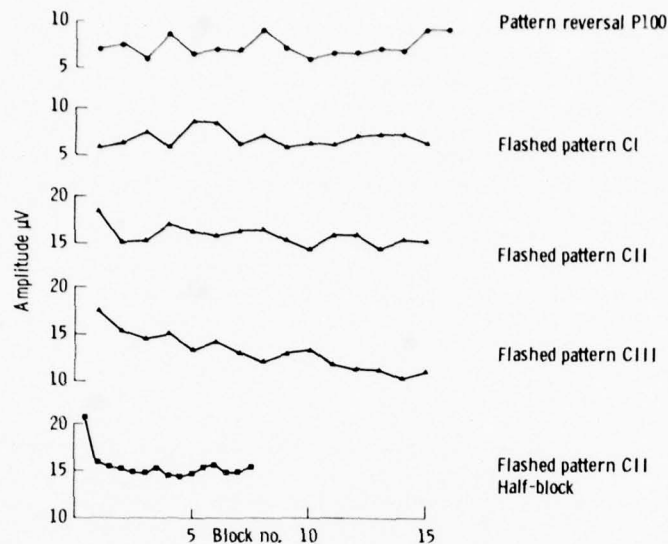


Fig. 4. Variation in component amplitude during a long stimulus sequence for pattern reversal and flashed pattern VEPs. Each contiguous block contains 32 VEPs. For the last graph there are 16 VEPs per block, and these have been plotted as "half blocks" to preserve the time scale for the figure.

are not shown separately. For reversal VEPs the P100 component remains unchanged over the long sequence. For pattern onset and flashed pattern VEPs CI shows no overall change in amplitude, and this is independent of check size. CII shows a gradual decrease in amplitude which is described reasonably well by an exponential function (correlation coefficient 0.96). The rhythmical superimposed fluctuations were more marked for pattern onset VEPs and increased in amplitude with time; they may be due to variations in attention. CII shows a sharp initial drop and then remains essentially constant. This is clearly visible for each check size for each subject. A block size of 32 is a rather coarse measure, and so one set of data was recalculated for blocks of sixteen (smaller blocks than this give inadequate signal enhancement). The initial amplitude drop and subsequent stabilization become more apparent.

DISCUSSION

The main findings from this work are that the amplitude of each component of the averaged VEP is affected to some extent by the temporal properties of the stimulus regime; since they are differ-

entially affected, changes in waveform are produced. The behavior of CI may be explained in terms of saturation induced by residual contrast; CI does not appear to be subject to adaptation at all. CIII adapts slowly, and the effects of this are visible only after a fairly large number of stimulus presentations. The behavior of CII is quite different: it adapts quickly and reaches a stable, and considerably reduced, amplitude in a small number of presentations. These findings are in general agreement with those of James and Jeffreys (1975) but differ in the degree of attenuation found in CIII. This may be due to the length of pre-exposure used; a long pre-exposure would increase the adaptation of CIII relative to CII. An alternative explanation is suggested by Jeffreys' data (1977) from which it appears that CIII amplitude is relatively constant except for a single condition (100% contrast, 25 msec duration), which may be anomalous.

A number of other studies have produced results which are compatible with the residual contrast model, although comparisons of data can only be made with caution as most previous work has been carried out on flash VEPs, often with different electrode placements and invariably with peak to peak measures of amplitude. Differences between vertex and occipital VEPs were pointed out by Lehtonen (1973), particularly for CII (his N3). He also noted that this component increased in amplitude in the presence of stimulus contour. In fact, the amount of contour used - simply the rectangular boundary of the stimulus screen - was very small and approximates to the blank flash stimulus used in the present study. This does emphasize the point that, although the difficulties of producing a pattern VEP uncontaminated by luminance components are well known it is also difficult to produce a luminance VEP free of pattern components. Hence many supposedly flash VEPs do contain recognizable contour components, in some cases enough to permit comparisons with pattern VEPs to be made. An initial peak similar to that ascribed to residual contrast in the data presented here is present in the data of Mecacci and Spinelli (1976) who measured VEP amplitude (steady state, sinusoidal grating, reversal VEP) as a function of recovery time after adaptation to a similar high contrast pattern. Residual contrast may also be involved in the enhancement of VEP by pre-exposure to conditioning (adapting) lights, which was described by Kitajima et al. (1975). Although their data relates to flash VEPs a component corresponding to CII is clearly visible and markedly affected by adaptation. An effect due to stimulus regularity is indicated, but its origins are not resolved. The effects of attention and expectation on EP amplitudes are well documented (e.g., Squires et al., 1976), and in this study CII amplitude for long interstimulus intervals was modified by controlling temporal uncertainty. However, psychological variables seem unlikely to be involved for the early parts of the graphs. The value of inter-stimulus interval at which the slopes change is not correlated with any subjective temporal performance criteria such as an instant-

neous/durable transition (Serviere et al., 1977), optimum interval estimation (Woodrow, 1934) or loss of sense of rhythm (Fraise, 1956), whilst it is increased by an increase in previous adaptation time. Hence a physiological explanation is indicated. If the contention of Basar et al. (1975), that EPs mostly result from frequency stabilization of spontaneous activity, triggered by stimulation, is correct, then this may reflect the different effectiveness of regular as opposed to irregular stimulation in frequency stabilization. The findings from the long stimulus sequences confirm the predictions of component behavior derived from the data of the short term experiments, and other authors have demonstrated similar results (for example, Armington, 1964; Laurian and Gaillard, 1976; Shipley and Hyson, 1977). Shipley and Hyson discuss the shape of the attenuation curve (for various modalities) and suggest that it becomes more nearly a duplex function as stimulus rate is increased. Our results show that for pattern VEPs the initial decrease will be steeper for shorter interstimulus intervals accentuating the break between the CII-dominated and CIII-dominated parts of a curve of peak-to-peak amplitude. This is in agreement with their suggestion.

These results show what is well known to anyone who has watched VEPs being averaged: the first response is invariably much larger than subsequent ones, and the conclusions to be drawn are of practical significance. Attempts to choose temporal stimulus parameters, such that the measurement procedure itself produces no adaptation effects on the VEP, are likely to be unsuccessful. Generally CI will exhibit no adaptation effect, and CIII little. CII, on the other hand, will be subject to rapid initial adaptation, and the use of a very long interstimulus interval to avoid this will increase the likelihood of psychological variations, to which this component is also shown to be subject. A practical procedure would be simply to discard the VEPs to the first six or so stimuli. In this way a stably adapted VEP will be obtained.

SUMMARY

The effect of adaptation-type processes upon the waveform of the transient visual evoked potential (VEP) was investigated in normal subjects using flashed pattern, pattern onset and pattern reversal stimuli. A checkerboard pattern was used with check sizes of, variously, 15', 30' or 60' of arc. Changes in amplitude of the individual components of the VEP were measured as a function of stimulus duration and interstimulus interval (flashed pattern and pattern onset) or stimulus period (pattern reversal). For pattern onset VEPs both regular and random interstimulus intervals were used. Each component was shown to have some dependence upon temporal stimulus parameters, although a marked adaptation effect occurred for only one. The variation in component amplitude as a function of interstimulus interval had, in each case, a bifid form, indicat-

ing the involvement of more than one physiological process. There was also some dependence upon check size. The findings were used to describe the behavior of component amplitude in an averaging run, and the validity of this description was tested by investigating variations occurring during a long stimulus sequence.

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LINGUISTIC MEANING-RELATED DIFFERENCES IN ERP SCALP TOPOGRAPHY

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Certain aspects of language have been hypothesized to be processed in different cortical areas or, at least, by different neural elements. The most obvious example is the classical differentiation of the speech disorders associated with frontal or temporal-parietal lesions of the dominant hemisphere, i.e. expressive versus receptive language disorders. More specific disturbances have been reported which showed impairment of word finding predominantly concerning nouns in some patients and verbs in other patients (Kleist, 1934; Brown, 1972). Nouns and grammatical words have been reported to be differentially affected by anterior and posterior lesions in patients with anomia (Brown, 1972).

Recent research (Brown et al., 1973; 1976, in preparation; Marsh and Brown, 1977) has shown that different contextual meanings of homophone words evoke waveform differences in scalp recorded event related potentials (ERPs). For example, responses to the word /'led/ in the ambiguous phrase "it was /'led/" differed reliably depending on whether subjects had been instructed to perceive the stimulus word as "led" or "lead". Principal component analysis of the data from this experiment showed that individual components of the evoked responses exhibit maximal differences between word meanings at different electrode sites (Brown et al., in prep.). These data indicate that the evoked potential correlates of the processing of meaning in speech are a complex interaction between the particular ERP component, its amplitude and scalp topography.

The present paper investigates the scalp topography of responses evoked by different meanings of homophones. In the simplest case, the activity of different neural populations involved in processing

homophone nouns and verbs would be reflected by different locations of maximal and minimal values of evoked scalp EEG fields. The main features of EEG scalp fields are simple (Lehmann, 1971; 1977; Lehmann et al., 1978; Ragot et al., 1976). Their principal characteristics at a moment in time can be described by the location of the maximal and minimal field values (Lehmann, 1971; 1977).

One important advantage of the study of ERP topographies, rather than waveforms recorded at individual electrodes, is that the problem of the reference electrode can be avoided. The location of the field maximal and minimal values and the gradients within the field are not influenced by the choice of reference electrode. Only the average field value will be affected by the reference. Thus, analyses which utilize locations of extreme field values or other aspects of the topography are unambiguous relative to the behavior of the reference.

We chose to investigate the topographical differences evoked by noun-verb homophones when given specific meaning by the context of the sentence in which they occur. In order to ensure that the results would be generalizable to verbs and nouns in different languages, one stimulus paradigm was English and the other Swiss-German: "a pretty rose" and "the boatman rows"; and "e schöni chlini Flügge" (a pretty little fly) and "en Vogel chunnt z'flügge" (a bird comes flying). The meanings of "rose" and "flügge" in these two pairs of sentences not only contain noun-verb syntactic differences, but also connotative meaning differences (e.g., quiet-active states).

The test sentences were tape recorded, and the same stimulus word, with an associated trigger pulse on a second channel, was spliced into the two sentences from each paradigm. This ensured that the homophone words in each sentence pair were exactly the same physical stimulus. A tape loop was used for recording repetitive sentence presentations.

To rule out any effects caused by acoustic differences between that portion of the test sentences which preceded the stimulus word, a blurred but speech-like modulated tone sequence was produced, i.e., a 500 Hz tone was amplitude modulated using a rectified and low pass filtered original test sentence. The resulting sound sequence was not understood by six different evaluators: upon suggestion of wordings ("e schöni chlini Flügge" or "en Vogel chunnt z'flügge") either wording was judged to be equally likely. Thus, depending on the instructions to the subject, the identical degraded speech stimulus could elicit a noun or verb interpretation. Hence, any differences in brain responses to the imagined meanings must be exclusively cortical responses.

The 21 subjects were all right-handed, healthy females (age 18-35). The English sentences were presented to seven native English speaking subjects and the Swiss-German sentences, as well as the blurred sentences, to native Swiss-German speaking subjects (seven in each group).

Electrodes were attached in a transverse 3 X 4 array, centered around the vertex with 5 cm between electrodes (Fig. 1). Additional electrodes were attached on the two earlobes, the outer canthi of the eyes and in eleven subjects, above and below the left eye. EEG data from the scalp and left ear were recorded in thirteen channels against the right ear and lateral and vertical eye movements were recorded on two additional channels. A bandpass of 0.3 to 70 Hz (6 db down) was used. The A/D rate was 256 s/sec. The data for each run were averaged on line.

After electrode attachment, the subjects were comfortably seated in an electrically shielded and sound-attenuated chamber and instructed about the experiment. They were asked to listen to the sentences, and particularly to attend to the meaning of the test words in the specific sentence context. Subjects were also asked to keep their eyes closed during recordings. A loudspeaker was positioned 1.5 m behind the subject. There was a low level continuous background random noise (50-2000 Hz). The sentences had a peak intensity of 70 db at the subjects' ears. In each recording run a sentence was presented thirty times (4.6 sec cycle time for the English and 5.0 sec cycle time for the Swiss-German and degraded sentences). After a pause of 2.5 min, the next run presenting the other sentence was begun, and so on until each sentence had been used in seven runs. On each run, the subject was told via intercome to get ready for sentence presentation, and data collection was started after the first sentence.

For each subject, evoked potentials in all channels were averaged ($N=30$) during seven runs with each of the two stimulus sentences (seven runs with each meaning in the case of the degraded speech stimulus). The averaging procedure was started at the onset of the homophone word, using the trigger pulse on the audio presentation tape. Average evoked potentials to words in sentence context, although small, have identifiable waveforms (Fig. 2). Each of the resulting fourteen sets of twelve scalp recorded averaged evoked potentials was transformed into sequences of maps of scalp field distributions (see examples in Fig. 1) for forty analysis times in intervals of 15.6 msec between 33 and 642 msec after stimulus onset. In each field map, the location of the electrode with the maximal and minimal potential value was determined. For further data analysis, only this reference-free information on location was used.

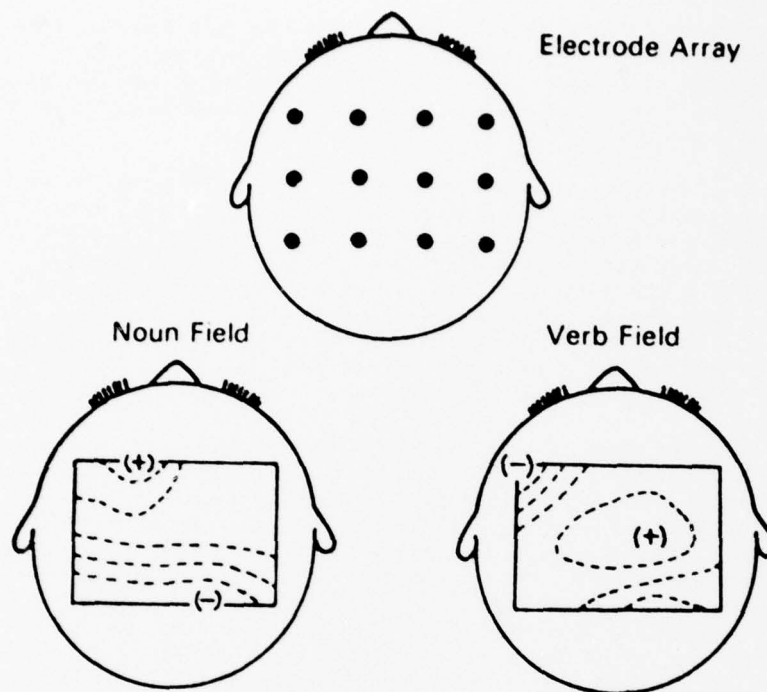


Fig. 1. Scalp electrode array (interelectrode distances of 5 cm) and sample scalp field distributions evoked by noun (left) and verb (right), 126 ms after word onset. Fields are a mean of 210 responses in one subject. Field lines are linearly interpolated between electrode positions. Note maximal and minimal field values ("+" and "-", respectively).

The median location among the seven runs in each condition was separately computed for field maxima and minima. Medians were thus computed for each subject, each condition (noun/verb), and each analysis time (196 medians per experiment). These median field locations represent the spatial center of the cluster of maximum or minimum locations from the seven runs of each meaning condition. Since we wanted to examine the differences between noun and verb related scalp fields, the topographical relationships between noun and verb extreme value locations were plotted in a coordinate system. The position of the verb median location was plotted relative to the noun, i.e. the noun location was set at the origin. For each analysis time, in each of the three experiments, the median locations of the seven subjects were entered into separate plots for maxima

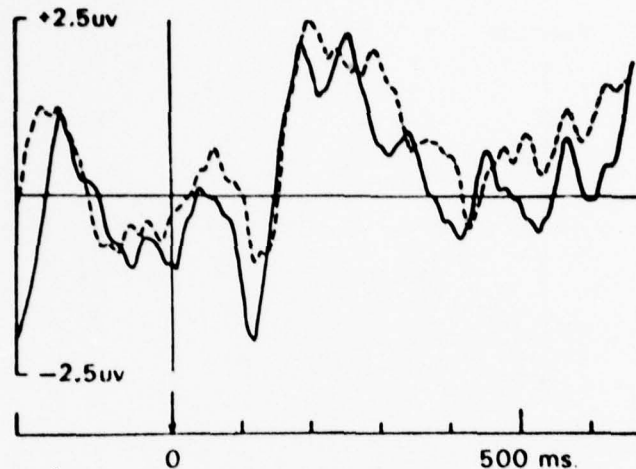


Fig. 2. Average potential waveforms evoked by "rose" (solid line) and "rows" (dotted line). Responses are a mean of seven subjects, 210 responses from each subject. Responses shown were recorded between the scalp electrode in the second row in the second column, and the right ear (as illustrated in Fig. 1). Arrow indicates the onset of the stimulus word.

and minima (see example in Fig. 3).

To summarize across subjects the relationship between locations of the extreme (maximum and minimum) values of noun and verb fields, a spatial discriminant analysis was performed. A vector was rotated through the origin of the coordinate system in order to determine the line which best divided the plot into two halves, of which one contained a maximal number of observations (see Fig. 3). The vector angle which produced the highest sum of signed ranked distances and the highest sum of signed distances of the plotted relative verb locations from the vector was determined by an iterative procedure and used as descriptor of the average field relationship across subjects. Significance of the resultant discrimination was determined by a Wilcoxon test of ranked distances.

For each group, the discriminant vector angles of all analysis times can be seen in Fig. 4. As this figure demonstrates, the three subject groups show similar results. The sum of all the entries during the entire analysis period (histograms at the bottom of each graph of Fig. 4) indicates a predominant angle of about

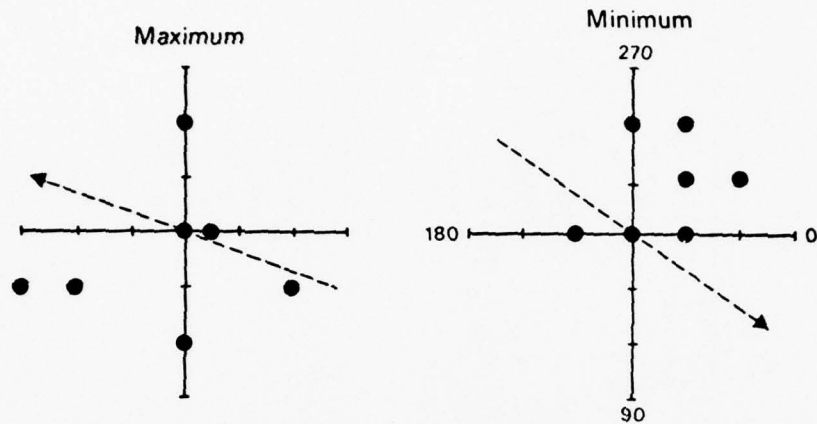


Fig. 3. Relative positions of maximal (left) and minimal (right) values of verb fields (dots), plotted in spatial reference to noun field maximal and minimal values (at origin of coordinate systems). The data are median locations of maximal and minimal values in each of the seven subjects of one experimental group at analysis time 126 msec after word onset. Scale markers indicate one interelectrode distance. Dashed line with arrow shows the discriminant angle. Significance of the discriminations shown are $p = .249$ for maxima, and $p = .046$ for minima (Wilcoxon tests, one tailed). (From Brown and Lehmann, in prep.)

180 degrees for maximal field values, and approximately 0 (or 360 degrees for minimal values, although there is considerable variance at different analysis times.

The 180 degree angle indicates a posterior location of the verb maxima referred to the noun maxima, and the 360 degree angle for minima, the opposite relationship. Chi-square tests for non-randomness of the histograms at the bottom of Fig. 4 were significant for all three groups for the minima (English and Swiss, $p < .001$; Imagined, $p < .01$) and two of the three groups for the maxima (English, $p < .02$; Imagined, $p < .01$; but Swiss, $p < .10$).

If we examine changes over time by summing over only ten analysis times across the three groups (Fig. 4, "All subjects") and test for significant departure of the distribution from a random distribution, it becomes evident that the locations of the maxima are clearly separate in the two stimulus conditions in an anterior-posterior direction (angles between 135 and 225 degrees) during about the first 174 msec after stimulus onset, and the locations of the minima are clearly separate in the opposite direction

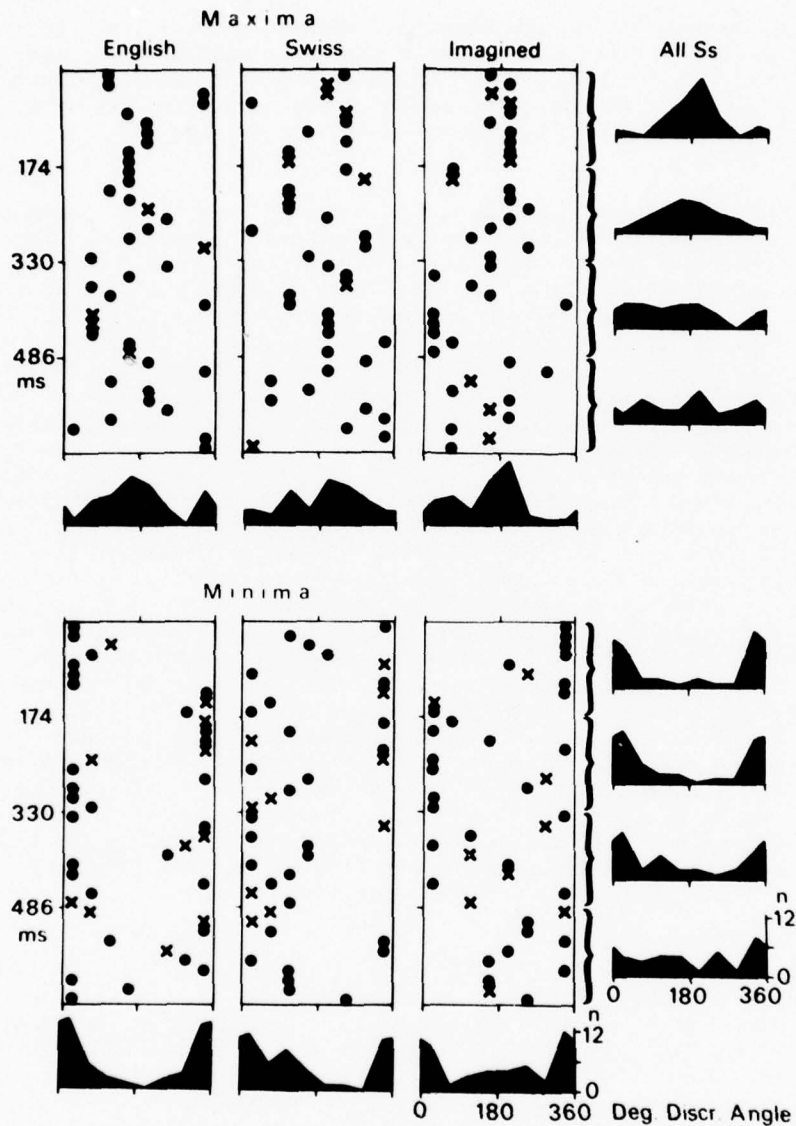


Fig. 4. Discriminant angles between relative scalp locations of verb and noun evoked maximal and minimal field values as a function of time (msec). Angles with $p < .06$ are indicated by crosses; $p > .06$, by dots. Distribution for all forty analysis times for each group are shown below as solid graphs, and for epochs of ten analysis times over all three groups, at the right. (From Brown and Lehmann, in prep.)

(angles between 315 and 45 degrees) during about the first 330 msec, after which the clear preference of the discriminant angles begins to fade. Chi-square tests for nonrandomness of these distributions were significant for the first epoch of the maxima ($p < .001$) and first three epochs of the minima ($p < .001$, $p < .001$ and $p < .02$, respectively).

One may suspect vertical eye movements as a possible source of anterior-posterior displacements of extreme scalp field values. The literature, to our knowledge, does not report on vertical eye movements being related to the perception of different word meanings. However, we recorded vertical eye movements from electrodes above and below the eye with the same amplifier settings as the evoked potential data from eleven subjects (three in the English, four in the Swiss-German and four in the Imagined sentence paradigm). The eye movement recordings were averaged over all noun presentations and over all verb presentations for each subject. Comparison of these traces demonstrated no significant differences at any of the forty analysis times, which excludes a possible role of presentation related eye movements in our results.

To more precisely observe the topography of ERPs to the noun and verb meanings of homophones, an additional subject was run while recording from 37 channels simultaneously. Electrodes were placed in a 7 X 7 matrix centered on the vertex, with the three electrodes at each corner of the matrix missing. Interelectrode distance was approximately 3 cm. This subject was a native English speaking female who listened to the English stimuli. All procedures were the same as those described above. That the data from a 37 electrode system in this subject confirm the results of the other subjects can be seen in Fig. 5. The noun meaning "rose" produced scalp fields in the early part of the response epoch which have an anterior positivity and posterior negativity. The verb meaning "rows" produced fields of opposite anterior-posterior slope.

The results obtained in the three experimental groups, as well as the 37 channel recording from the additional subject, demonstrate consistent differences in the locations of extreme scalp field values between the noun and the verb stimulus conditions. For the first 175 msec after stimulus onset, the maximal field value is more anteriorly located in the noun condition, and for the first 330 msec after stimulus onset, the minimal field value is more posteriorly located in the noun condition than in the verb condition. Apparently, the functional neural elements whose activity constitutes the evoked brain response to the stimulus word are not identical in our two stimulus conditions: a critical subpopulation is different for nouns and verbs. This may mean different locations or different orientations of the active elements.

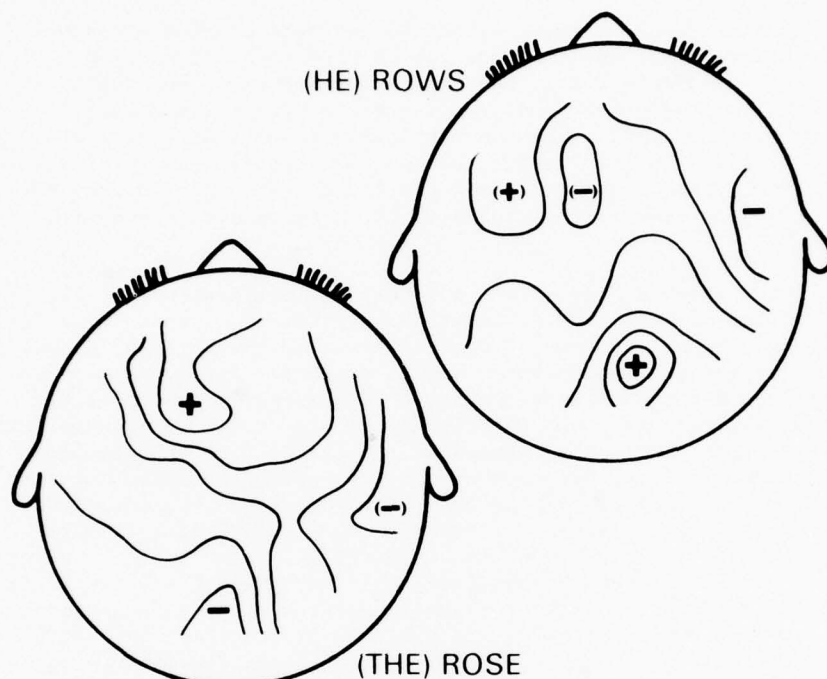


Fig. 5. Topographic maps of average ($N=210$ scalp fields recorded from a 37 electrode array in one subject while perceiving the English word /roz/ as a noun (labeled "the rose") and as a verb (labeled "he rows"). Field latency is 48 msec after onset of the word /roz/. Isopotential lines are linearly interpolated every $0.5 \mu\text{V}$. (From Brown and Lehmann, in prep.).

It appears that it is not the decoding process of the physical stimulus which is manifested in the evoked EEG activity, since the degraded speech sequence evoked results which, depending on the instructions to the subject, were comparable to those from understandable sentences. Rather, it is the syntactic or connotative meaning which is reflected by the evoked potential topography. Thus, different internally generated meanings are associated with evoked potential characteristics which are similar to those produced by the same meanings when they result from the decoding of speech information.

The topographical differences which we have demonstrated are constant over two different languages, using different specific sentence meaning and different stimulus word meanings. They are

also constant over at least two different sets of phonetic representations. The most obvious common difference of meaning between the two sentences in the three experiments is the verb-noun syntactic difference. However, other more general connotative features may be implied by the particular nouns and verbs which we used (i.e., passive/active, contemplative/strenuous, etc.). We note at any rate that it is language information which evoked the responses, whatever later stages of brain processing may be involved.

Other reports have shown that the internal presence of specific information or mental classification of stimulus content determined evoked waveforms independent of the nature of the physical stimulus. Using nonlinguistic paradigms, evoked potential differences related to different internal representation of physically identical or similar stimuli have been reported by John et al. (1967), Herrington and Schneidau (1968) and Lehmann et al. (1977). Evoked potential differences produced by somewhat more directly linguistic interpretations of similar stimuli have been reported by Johnston and Chesney (1974), Teyler et al. (1973), Grinberg and John (1977), Brown et al. (1973, 1976, in prep.), Marsh and Brown (1977). Chapman et al. (1978) have demonstrated that averaging responses across numerous words which share the same general semantic meaning results in responses whose waveforms are reliably affected by connotative meaning. Our approach of strictly topographical comparisons is unlike the analysis used in other evoked potential studies of language meaning. Therefore, direct comparisons with the results reported in the literature on meaning related language responses, are not possible.

The present paper uses strictly topographical data evaluation (Lehmann, 1971, 1977; Remond, 1968) and does not examine conventional evoked potential waveshapes (i.e., measurement of components of evoked potential waveshapes in time). The latter approach is used after an a priori decision that the data be treated in each channel separately, examining voltage differences between two recording points as a function of time. Accordingly, topography is a secondary consideration, usually dealt with indirectly. Contrariwise, our topographical analysis examines the data in all channels simultaneously as a function of space, and the time effects are evaluated in a second stage. An advantage of this approach is the avoidance of the classical problem in EEG analysis, the pre-selection of the recording points from which measurements will be compared. Also, as pointed out previously, the choice of the reference does not influence results of our topographical analysis. The particular tactics of topography applied in this paper imply considerable data reduction, i.e., reduction to location of maximal and minimal field values, but the principles of analysis would not

be different if one decided to use a more fine grain analysis of the scalp field structure, including the voltage difference between recording points.

SUMMARY

Three experiments were accomplished which compared the scalp field topographies of potentials evoked by the noun and verb meanings of homophones. Results were consistent in the three experiments. Locations of scalp field maxima were more anterior for nouns than verb meanings. Field minima for noun meaning were more posterior than verb minima. The effect for maxima lasted throughout the first 180 msec of the response, and for minima, throughout the first 230 msec.

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APPLICATION OF SOMATOSENSORY EVENT RELATED POTENTIALS TO
EXPERIMENTAL PAIN AND THE PHARMACOLOGY OF ANALGESIA

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INTRODUCTION

There is increasing evidence that many neurotransmitter systems may be involved in pain appreciation including cholinergic agents, endorphins, biogenic amines and others (Mayer and Price, 1976). This suggests that there are multiple mediators of pain appreciation, each involving a possibly distinct neural pathway. Event related potentials may offer a means of separating distinct pain modulation processes in pharmacological experiments in man.

The average evoked potential (EP) to electric shocks has been used in a number of psychophysiological studies of psychogenic pain (Mushin and Levy, 1974), pain predictability (Lykken et al., 1972), hysterical anesthesia (Moldofsky and England, 1975; Levy and Mushin, 1973) and cutaneous stimulation (Satran and Goldstein, 1973).

We have previously reported that individuals who appear relatively pain tolerant (on the basis of signal detection analysis of their subjective pain ratings) show somatosensory EPs which increase in amplitude less rapidly with increasing stimulus intensity than those of relatively pain intolerant subjects (Buchsbaum, 1975). Audioanalgesia was also associated with a reduction in the amplitude/intensity slope of the EP (Lavine et al., 1976). We have also reported that naloxone, a narcotic antagonist which reverses the effects of opiates and endorphins, alters pain sensitivity and EPs when administered alone to normal subjects, suggesting a physiological role for endorphins in pain regulation (Buchsbaum et al., 1977). In these studies, the positive component at 100 msec (P100) and the following negative component (N120) were the most consistently af-

fects, especially when recorded at C4 with contralateral stimulation.

In approaching other pharmacological interventions, including lithium, physostigmine and choline chloride where analgesia effects might possibly arise from a variety of mechanisms, we hoped that EP results might be especially valuable. By revealing distinctively different patterns of components and different topographic distribution, similarity of mechanisms might be identified.

In order to help clarify analgesic effects, experiments with a classic analgesic seemed crucial. Aspirin was chosen because of its safety and widely recognized efficacy. Taking the largest and most reliable aspirin effect as a criterion, different techniques of EP processing and peak measurement could also be compared for utility.

METHODS

Subjects

Forty-seven normal adult volunteers participated, fifteen (six men and nine women) in a test-retest reliability study and thirty-two (sixteen men and sixteen women) in a double-blind crossover study of aspirin.

Experimental Protocol

All subjects participated in an identical first session. This consisted of a psychophysical pain rating procedure followed by somatosensory evoked potential (EP) recording. No drug or placebo was given. Subjects were scheduled at their convenience between 8:00 a.m. and 4:00 p.m. Stimuli were administered and both psychophysical ratings and electroencephalographic responses recorded by an on-line computer.

Test-retest. For the test-retest analysis, this session was repeated on a second occasion, usually one to two weeks later.

Aspirin. For the drug trial, two additional sessions like the first were utilized. Subjects received either 1 gram aspirin or placebo orally in a randomized, counterbalanced design and then waited 60 min before beginning the psychophysical/EP session. Aspirin and placebo were administered in identical pink capsules from coded containers and analyses, including peak identification and statistics, were done before decoding the treatment.

Stimuli. Electrical stimulation was provided by a concentric electrode (Tursky) connected to an on-line computer controlled con-

stant current stimulator and placed on the dorsal of the left forearm. Each stimulus was a 1 msec biphasic pulse. Skin preparation and stimulation techniques are described in Lavine et al. (1976).

Somatosensory EP procedure. Four stimulus levels (2, 9, 16 and 23 mA were presented sixty-four times each at 1 sec intervals in a random order constrained so that each stimulus intensity was preceded by each of the others and itself an equal number of times. EEG was recorded from vertex (Cz-right ear) and somatosensory cortex (C4-right ear), amplified and filtered (flat bandpass 1--40 Hz; down 3 dB at 0.3 Hz and 42 dB at 60 Hz). EEG was sampled at 250 Hz for 500 msec, and responses to each intensity were averaged on-line.

Psychophysical shock procedure. Subjects received three shocks at each milliamperage increment from 1 to 31 mA for a total of ninety-three shocks in a random sequence at 2.5-s intervals. Subjects rated each shock in one of four categories: noticeable, distinct, unpleasant or very unpleasant. Signal detection analysis yielded two pain measures: a nonparametric analog of response criterion and a sensitivity level (Sitaram et al., 1977). The sensitivity measure has been associated with pharmacological analgesia (Chapman et al., 1973) and response criterion has been related to suggestion effects (Clark and Goodman, 1974).

EP measurement. The largest and most commonly occurring components in the EP configuration for both Cz and C4 leads are a sequence of positive negative and positive deflections at about 100, 120 and 200 msec (termed P100, N120 and P200). These components were identified by visual inspection by a person blind to drug status, and the latency from the stimulus was recorded. Peaks were chosen to be 1) as consistent as possible in latency across the four intensities and two sessions and 2) to be within 25 msec of the 100, 120 and 200 msec anchor points. Amplitude of the components was measured in two ways. First, the height in microvolts from a 32 prestimulus baseline was determined. Second, an area integration technique not dependent on visual identification peaks was used. EPs were divided into three time bands centered on P100 (76-112 msec), N140 (116-152 msec) and P200 (168-248 msec). EP amplitude was measured by calculating the area within the band. This was done by first removing the mean of the entire epoch from 32 msec prestimulus to 480 msec poststimulus and then calculating the mean of the absolute values of the EP time values for each time band. The amplitude/intensity slope was calculated by least squares regression using the four EP amplitudes in microvolts and the logs of the stimulus intensities in milliamperes.

EP data were then analyzed by using paired t-tests and by using two- and three-way ANOVA with repeated measures and trend analysis for the intensity dimension. For test-retest correlations and pre-

dicted analgesia effects where the statistical hypothesis is unavoidably unidirectional, one-tailed tests are used.

RESULTS

Test-Retest Reliability of EP

Test-retest reliabilities were calculated for both mean amplitude (across four intensities) and for the amplitude/intensity slope (Table 1). Both showed reasonable consistency over time; area measurements of amplitude appeared clearly superior to the baseline-to-peak technique, as we have observed elsewhere for visual EPs (Buchsbaum, 1976).

Effect of Aspirin on Psychophysical Ratings

Consistent with the expected analgesic effect, aspirin increased the error rate (a nonparametric analog of d') for the distinct/unpleasant dichotomy from 7.3 on placebo to 9.5 (paired $t = 2.69$, $p < 0.01$, one-tailed). Psychophysical results will be reported in detail at a later date.

Effect of Aspirin on Somatosensory EPs

Aspirin diminished the EP amplitude, especially for high intensity stimuli and for the N120 component (Fig. 1, left). This was confirmed statistically by paired t -tests on the amplitude/intensity slope measures ($t = 2.86$, $p < 0.005$) by two-way ANOVA with drug treatment and stimulus intensity as repeated measures for area measures Cz-N120 ($F = 7.97$, $p < 0.01$; 1,30 d.f., linear trend analysis) and for C4-N120 ($F = 5.62$, $p < 0.025$, quadratic trend analysis) and peak measures for C4-N120 ($F = 4.92$, $p < 0.005$, quadratic trend analysis). Baseline-to-peak measure P100 also showed a main effect of aspirin ($F = 5.54$, $p < 0.05$). Area measurements showed that individual differences in the effects of aspirin were similar for both N120 and P200 (Table II), when amplitudes of EPs for the highest stimulus intensity were used.

Removal of Low Frequency Components

Both baseline-to-peak and area integration techniques could have their measurements distorted by sustained potentials, CNV or large P300 components which could affect baselines. Effects actually due to these slow components might hypothetically be attributed to earlier components such as P100 or N120. Late slow components appear minimal in the passive paradigm used here (Fig. 3), and base-

TABLE I

Test-Retest Reliability of EP Components

Lead	Peak	Technique			
		Area Mean	Scope	Baseline-to-peak Mean	Slope
Cz	P100	.50*	.43*	.56*	.06
	N120	.70*	.67*	.75*	.17
	P200	.85*	.89*	.77*	.74*
C4	P100	.05	.46*	.57*	.47*
	N120	.53*	.62*	.39	.21
	P200	.92*	.87*	.62*	.65*

* $p < 0.05$, one-tailed

Mean is calculated from amplitude at the four stimulus intensities; amplitude/intensity slope is calculated as described in text.

TABLE II

Correlation Between Area and Baseline-to-Peak Measure Effects of Aspirin

Amplitude of highest intensity EP	Lead	
	Cz	C4
P100	-.38	-.19
N120	.34*	.62**
P200	.47**	.68**

* $p < 0.05$, one-tailed** $p < 0.0025$, one-tailed

Change scores for placebo minus aspirin were calculated for each peak and lead in the two measurement systems.

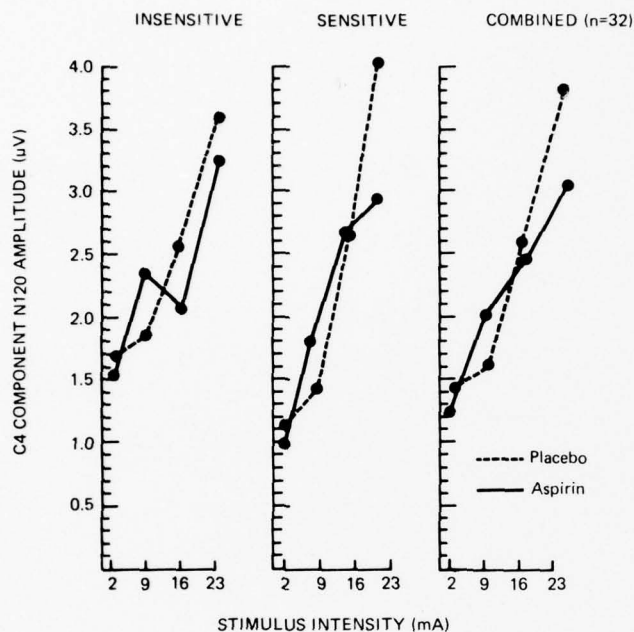


Fig. 1. Mean evoked potential amplitude in μV for negative peak N120 at four stimulus intensities for pain sensitive ($N = 15$), pain insensitive ($N = 17$) and total groups ($N = 32$). Solid lines are aspirin, and dotted lines are placebo. EP differences at highest intensity are consistent in the two subgroups. Drug X intensity interactions were confirmed by ANOVA statistically, but group X drug X intensity interactions were not significant. Note that sensitive individuals on placebo have greater amplitude/intensity slopes (augmenting) than pain insensitive individuals.

line shifts due to the intensity of the preceding stimulus cannot systematically influence stimulus intensity effects because of the stimulus intensity randomization used. Nevertheless, for a rigorous test all EPs were filtered using a high pass autoregressive filter (Coppola, in press) with a filter constant of 0.93 yielding a 50% amplitude value of 2.5 Hz (Fig. 2). This filtering only minimally altered aspirin effects; for area measurement of Cz-N120, the F-

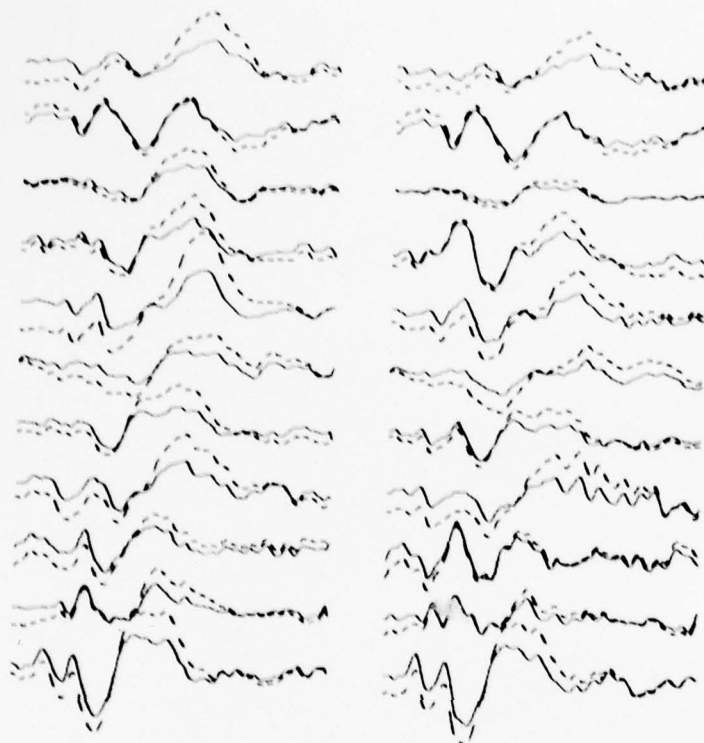


Fig. 2. Effect of high pass autoregressive filter on EP waveform. EPs for 33 mA stimulus, C2 lead on the left and C4 on the right, for the eleven subjects with typical EPs in Fig. 3. Curves before filtering (dotted) and after removal of low frequencies (solid) are illustrated. Note that while P200 is somewhat attenuated, early components are minimally affected. No P300 is evident in these subjects.

ratio for the drug \times intensity effect increased from 7.97 to 11.7. P100 peak-to-trough effects were also enhanced. C4-N120 F-ratio values were somewhat diminished, but the aspirin-placebo *t*-tests on the amplitude of the highest intensity EP remained statistically significant. Thus not only did low frequency components not appear to be the source of the EP changes, but their removal was mildly advantageous for the vertex EP.

Psychophysical and EP Correlations

Individuals who responded to aspirin by showing an analgesic effect on the psychophysical procedure (error rate increase) tended to show analgesia on the EP measure, the C4-N120 amplitude/intensity slope. The correlation between the placebo minus aspirin change scores for the C4-N120 amplitude/intensity slope and distinct/unpleasant error rates was 0.382 ($p < 0.05$) for the twenty-five individuals with complete psychophysical range data. The baseline-to-peak mean P100 measure correlation was 0.481 ($p < 0.01$).

Individual Variation in Pain Sensitivity and Aspirin Effect

In our studies of naloxone (Buchsbaum et al., 1977) individuals who were particularly pain insensitive on the baseline day were especially likely to show naloxone-induced hyperalgesia. Using the same pain sensitivity level used in the naloxone study as a criterion, subjects were divided into pain sensitive and pain insensitive groups on the basis of their baseline day psychophysical pain ratings. In this study no statistically significant interaction effects were seen, both pain sensitive and pain insensitive groups sharing aspirin-induced diminution of high intensity EP amplitude. Note that as we have previously reported, pain sensitive individuals had higher amplitude/intensity slopes (augmenters) on the placebo day than did pain insensitive individuals (reducers). This was statistically confirmed for the C4-N140 intensity function (group by intensity effect, $F = 4.76$, $p < 0.05$) and was present as a trend for Cz-P100 and C4-P100.

Individual Differences in EP Configuration

Within the thirty-two individuals there was variation in the appearance of the EP even on placebo. Some individuals showed a typical triphasic vertex EP, similar to visual EPs, with a positive peak at 80-110 msec followed by a clear negative-positive sequence at 120 and 220 msec. A second group showed an earlier positive component usually at 40-60 msec, an earlier negative at 70-80 msec and a typical latency positive at 220 msec. A third group showed variable or absent P100, most frequently dropping out at the highest intensity. The three groups, sorted on their placebo EPs, are illustrated in Fig. 3. Note that the early and variable groups showed considerable consistency in waveform from session to session, mitigating against recording artifacts being the source of the distortion or loss of P100. The typical group showed the greatest aspirin effect, the P100-N140 complex almost disappearing in some cases. Ten of the eleven individuals with typical EPs showed area amplitude/intensity slope reduction for C4-N120 with aspirin and ten of the eleven also showed diminished baseline-to-peak P100 amplitudes.

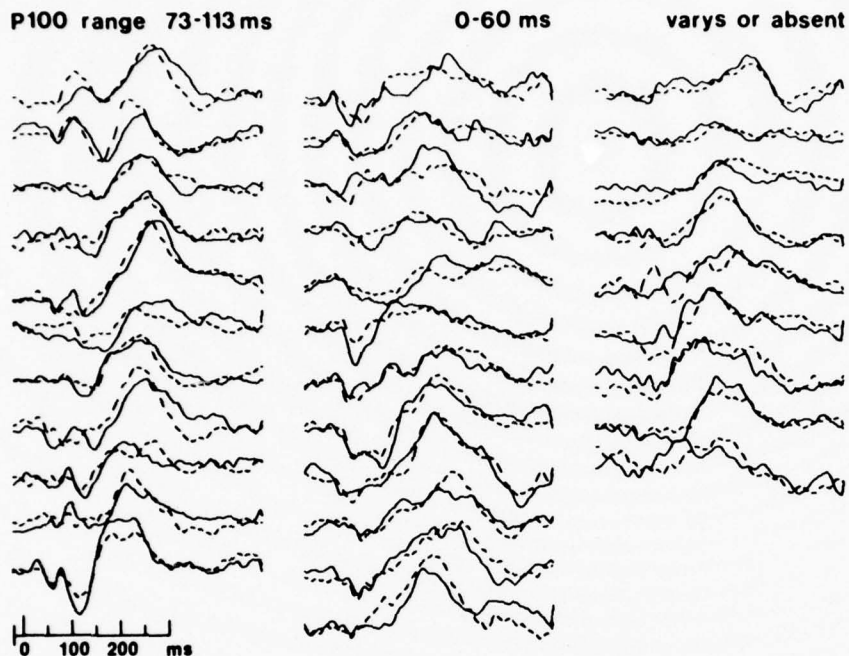


Fig. 3. Grouping subjects by P100 configuration and latency. EPs for 23 mA stimulus, Cz lead are shown, positive up, for all thirty-two subjects on placebo (solid line) and aspirin (dotted line). Left: subjects selected for clearest P100 at all stimulus intensities in the usual (73-113 msec) range while on placebo. Note aspirin diminution of P100 and N120 components. Middle: subjects with a very early positive component and no 100 msec positivity. Right: subjects who showed variable or absent early components making assessment of stimulus intensity curves difficult.

This is seen statistically in the F-ratios for area C4-N210 for the typical, early and variable groups which are 10.45, 3.35 and 4.16, respectively (drug-by-intensity interaction linear trend effect). Peak identification was helpful, and the baseline-to-peak Cz-P100 measure yielded F-ratios of 7.97, 7.56 and 4.77 (drug effect). Thus it appears that the early group may indeed have physiologically similar activity at a shorter latency. Both the typical and early groups had larger baseline-to-peak P100 amplitude at C4 than at Cz, consistent with the topographic findings of Goff et al. (1977).

DISCUSSION

In this study somatosensory EP amplitude and amplitude/intensity slopes parallel psychophysical rating changes with aspirin, both techniques confirming aspirin analgesia. The statistical strengths of the two techniques, as measured by the paired 't' values comparing aspirin and placebo were similar, being 2.69 for the nonparametric analog of d' and 2.86 for the area Cz-N120 amplitude/intensity slope.

Individual differences in analgesic effects of aspirin were reflected in significant correlations between the magnitude of the changes associated with aspirin in psychophysical and EP measures. Variability in the analgesia effect of aspirin was reduced by choosing individuals with typical triphasic EPs, and more consistent effects were observed than those achieved with the psychophysical measure used.

The analgesia associated with aspirin appears distinct in origin from that found with physostigmine. While both showed a distinct/unpleasant error rate increase on the psychophysical task, physostigmine showed exclusively P100 and P200 effects, whereas for aspirin, like naloxone, the C4-N120 effect predominated. We have suggested (Sitaram et al., 1976) that physostigmine analgesia effects may be mediated by arousal mechanisms. In contrast, the association of P100 and N120 reducing seen with aspirin analgesia and with audio analgesia seems more related to trait differences in pain sensitivity. As we have earlier noted, augmenting P100 or N120 amplitude/intensity slopes are related to pain sensitivity on placebo or baseline sessions (Buchsbaum, 1975; Buchsbaum et al., 1977). Additionally, naloxone, a drug which showed no total group effect on the psychophysical measure, produced augmenting on the N120 component in pain tolerant individuals, suggesting that individual differences in endogenous opiates might be reflected in the P100-N120 complex (Buchsbaum et al., 1977). The grouping observed here of aspirin effects with endogenous opiate effects is intriguing. Further development of EP techniques with measurement of primary P30 and P50 components, and testing of a greater range of analgesics and neurotransmitter strategies as well, may be helpful in increasing the neurophysiological/neurochemical correlations.

It is noteworthy that physostigmine and aspirin were indistinguishable analgesics on the psychophysical task, and no significant group effect appeared with naloxone; yet EP results differentiated the first two agents and revealed individual differences in response for the third. This greater specificity of the EP measures, combined with its reliability, suggests the utility of somatosensory EP recordings in psychopharmacological investigations.

SUMMARY

Forty-seven normal subjects were tested on psychophysical and somatosensory evoked potential pain procedures during double-blind placebo controlled trials of aspirin. Two runs of electrical stimuli were presented to each subject's forearm using the Tursky electrode; 1) ninety-three shocks of random intensities were judged noticeable, distinct, unpleasant and very unpleasant and 2) four intensities of stimuli were used to record ERPs from vertex and C4 leads. Psychophysical pain sensitivity was assessed by nonparametric signal detection analysis. ERP component latencies were identified visually in the ERPs, and amplitude was measured both from a prestimulus baseline and peak-to-trough; area integration measures were also obtained for comparison. Both ERP and psychophysical pain ratings showed stable individual differences; test-retest correlations for occasions two weeks apart ranged from $r = 0.5$ for psychophysical tasks to $r = 0.7 - 0.9$ for amplitude and amplitude/intensity slopes. N120 components recorded from both C4 and vertex were especially sensitive to aspirin analgesia, significantly diminishing in amplitude and shortening in latency especially at higher intensities. Pain ratings also showed analgesia for the sensitivity measure (d' analog). Comparing aspirin results with previous data on naloxone, the N120 component was most consistently influenced by pharmacological analgesia; both P100 and P200 were also affected by time of day and individual differences in pain sensitivity. Taken together, these results indicate the practical utility of ERP methodology in neurobiological pain research.

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HEMISPHERIC DIFFERENCES IN EVOKED POTENTIALS TO RELEVANT AND
IRRELEVANT VISUAL STIMULI

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Since the early days of averaging evoked potentials (EPs) in man, the importance of cognitive variables, as well as stimulus variables, has been recognized (e.g., Chapman and Bragdon, 1964). Using an experimental design which involves processing number and letter stimuli, we have been studying EP effects related to a variety of cognitive operations (Chapman, 1965, 1966, 1969a, 1969b, 1973, 1974a, 1974b, 1977, in press; Chapman et al., in press (a); Chapman et al. in press (b)). Most of our analyses have been for the CPZ scalp location (recorded monopolar on the midline one-third of the distance from Cz to Pz; reference was linked earlobes). It is of interest to study the cognitive effects at other sites, with a particular focus on the question of hemispheric differences and parietal-occipital differences.

A more complete description of the experimental design and discussion of interpretations for the present chapter is given in Chapman (1973). In that paper results are given for twelve subjects for midline electrodes located over the central-parietal (CPZ) and the occipital area (Oz), as well as control data for EOG and alpha EEG. The present experiment provides comparable data for eight subjects for laterally located electrodes over parietal (P3 and P4) and occipital (O1 and O2) areas and permits an evaluation of hemispheric differences in the information processing tasks. In general, comparable information processing effects were found in both experiments. The evaluation of location differences was facilitated by the addition of control EPs to blank flashes and the use of additional analysis procedures, featuring discriminant analyses.

Earlier work on hemispheric specialization has been critically reviewed by Donchin et al. (1977). A caveat should be noted in

considering hemispheric differences, or any brain localization effects, from EP data. EP effects localized at some scalp site do not necessarily mean that the adjacent brain region is responsible for those processes. Because the measure is a voltage difference in an electrical field of a conducting medium, the orientation of the source, as well as its distance, are important. Far field effects have been demonstrated for early auditory potentials (Jewett et al., 1970). The importance of source orientation is illustrated by scalp localizations opposite to brain hemisphere in visual field studies (Halliday et al., 1977). Incidentally, the same problems exist for electrical recording within brain structures as for scalp recording. Given this caveat, the spatial localization interpretations given in this chapter, strictly speaking, refer to particular scalp sites (with ear reference) and should be extended to brain localization with great caution.

Another problem relates to the assumption that larger EP amplitudes signify more processing. We suggest a method of analysis here which avoids this assumption, at least in its usual simplistic form. The method is based on discriminant analyses which focus on variations of EP measures which maximally discriminate particular conditions. This approach does not rely on sheer amplitude, but rather seeks combinations of amplitudes, large or small, which most systematically covary with particular sets of experimental conditions.

EXPERIMENTAL PROCEDURE

Two numbers and two letters were flashed individually in random order at intervals of 3/4 sec preceded and followed by a blank flash. The subject's task was to compare numerically the two numbers on number-relevant runs, the letters being irrelevant to the task. On the other half of the runs the numbers were irrelevant, and the task was to compare alphabetically the two letters. By appropriately moving a momentary two-way switch at the end of each trial, the subject indicated whether the first or second number was larger on number-relevant runs and similarly indicated the alphabetic order on letter-relevant runs. The subject had a 1.5 sec time slot following the last flash in which to answer before the next trial started. Correct answers produced a tone; wrong answers produced a buzz. The number and letters were randomly selected (1-6, A-F), and the sequences of numbers and letters were randomized. Nearly every stimulus was processed appropriately by the subjects, with a performance accuracy of better than 99%. All stimuli were flashed at the same spatial location by a Bina-View display equipped with a Grass strobe (flash duration < 10 msec).

The stimulus processing demanded by the task depended on a

number of factors, including whether: (i) number or letter stimuli were task relevant, (ii) the number or letter class of stimulus could be anticipated and (iii) the character was the first or second relevant stimulus of the pair to be compared. For the first relevant stimulus in each trial, the information had to be stored by the subject until the second relevant stimulus occurred, after which the comparison could be made.

While the subject was performing the letter or number comparison tasks, electrical brain activity (EEG) was recorded from scalp electrodes at P3, P4, O1 and O2 (referenced to linked earlobes). Frequency bandpass was 0.3 to 70 Hz; 102 samples at each 5 msec interval were obtained beginning 30 msec before each stimulus. The data were collected from eight right-handed subjects (five male, three female) over a series of six sessions each.

By averaging the brain activity evoked by stimuli for similar conditions, separate averaged evoked potentials (EPs) were obtained for sixteen information processing conditions: relevant and irrelevant numbers and letters at four intratrial positions. From trial to trial the first number (or letter) stimulus occurred in intratrial positions 1, 2 or 3, while the second number (or letter) stimulus occurred in intratrial positions 2, 3 or 4. To simplify interpretations certain EEG data were discarded, so the EPs for intratrial positions 1 and 2 were based only on the first number and letter stimuli presented within each trial, while the EPs for intratrial positions 3 and 4 were based only on the second number and letter stimuli presented within each trial.

Even the irrelevant stimuli in this experiment must be processed to a certain extent to determine that they are irrelevant. The subject cannot anticipate whether the stimulus will be a letter or a number, and hence relevant or irrelevant, except in intratrial position 4. To provide a control with even less processing by subjects, runs were added in which only blank flashes occurred. The blank flashes were provided by the same Bina-View device and appeared as an illuminated rectangle. The trials for those runs had the same temporal structure as the letter-number trials: blank flashes at the 4 intratrial positions, preceded and followed by a blank flash, all spaced $3/4$ sec apart.

Each run contained 102 trials, each with four intratrial positions. Each subject was given ten number-relevant, ten letter-relevant and four blank runs spaced over a number of sessions. Averaging across all runs, the EPs for each subject were based on the EEG responses to 272 to 510 stimuli. This yielded twenty EPs for each subject: relevant and irrelevant numbers and letters and blanks for each of the four intratrial positions. For each electrode, the data set consisted of 160 EPs (20 X 8 subjects).

EP MEASURES

The EPs were measured in the manner described in Chapman (1973) in order to facilitate comparison with the midline results reported there. For each EP, five measures were obtained: mean amplitude over 480 msec, and 315 msec. The most global measure was mean amplitude over 480 msec relative to a baseline obtained at 0 msec (time of stimulus; the baseline was the average of four time points before and three after the stimulus). The amplitude at 105 msec, 225 msec and 315 msec were similarly measured relative to the same baseline at 0 msec. These measures index the amplitude at specified points within the EPs without the necessity of identifying particular peaks. The amplitude at 0 msec was measured relative to an arbitrary voltage level across the entire trial of four intratrial positions. The amplitude at 0 msec indexes CNV activity.

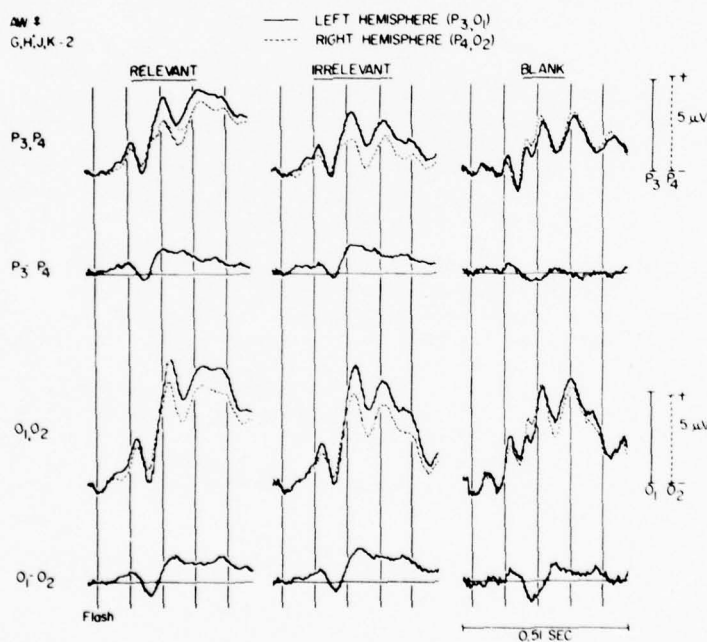


Fig. 1. Sample evoked potentials from one subject. Monopolar recording from left and right parietal (P3, P4) and occipital (O1, O2) scalp locations (referenced to linked earlobes). Vertical lines 100 msec apart.

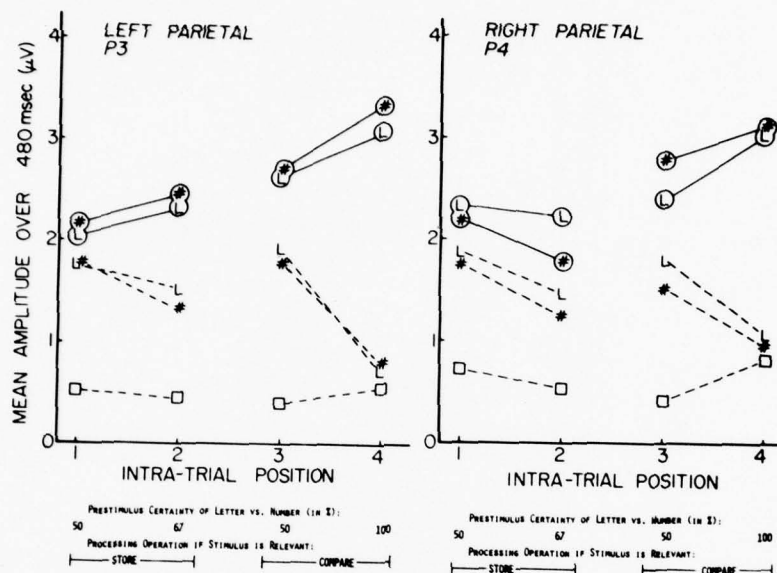


Fig. 2. Mean amplitude over 480 msec from left and right parietal electrodes for 20 experimental conditions with varying information processing demands. Number (#), letter (L) and blank (box) visual stimuli. Relevant (circled symbols and solid lines) and irrelevant (not-circled symbols and dashed lines). Information processing characteristics associated with intratrial positions are summarized below the abscissa. Data are means from eight subjects.

RESULTS

Fig. 1 illustrates some of the EPs for one of the subjects. For this figure, the EPs were averaged across numbers and letters and intratrial positions, in order to illustrate the hemispheric differences for relevant, irrelevant and blank stimuli. In this case the EPs from the left are larger than those from the right, and this hemispheric difference is greater for relevant and irrelevant stimuli than for blank stimuli. Drawing conclusions from the data of one subject may be misleading. To assess those effects which have more generality, the data for all eight subjects have been examined as a set.

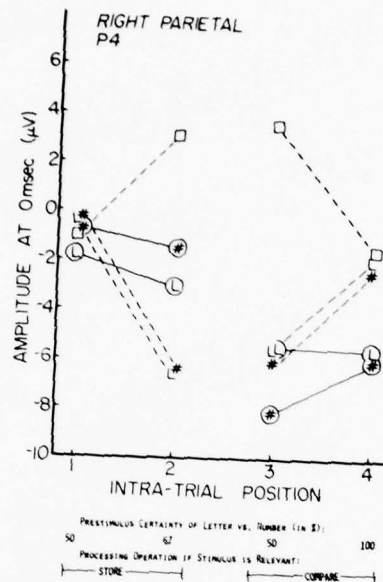


Fig. 3. Amplitude at 0 msec relative to an arbitrary voltage level which was the same for all responses. This measure indexes CNV. Other specification as for Fig. 2.

EP MEASURES FOR EXPERIMENTAL CONDITIONS

The results for mean amplitude over 480 msec are quite similar from left and right electrodes (P3 and P4 shown in Fig. 2) and are similar to those previously obtained from midline electrodes at Cp2 and Oz (Chapman, 1973, Figs. 3.6 and 3.7). The most striking result is the difference between relevant and irrelevant stimuli, regardless of whether numbers or letters were involved. There is also an interaction between relevance and intratrial position. In addition, the EPs to the blank flashes are considerably smaller than the responses to the number and letter stimuli. However, the EPs to the irrelevant numbers and letters in intratrial position 4, where there is 100% prestimulus certainty of stimulus class, approach the low amplitudes obtained to the blank flash controls.

Although there appear to be differences between the results for P3 and P4, the similarities dominate comparisons. The results for O1 and O2 (not shown) are also quite similar.

The amplitude at 0 msec showed a different pattern of relations to the experimental conditions (Fig. 3) which was similar to midline data previously reported (Chapman, 1973, Fig. 3.12). There were essentially no differences between relevant and irrelevant conditions at intratrial positions 1 and 3. At these positions there was a 50-50 chance of a letter or number occurring and, therefore, a 50-50 chance of the stimulus being relevant or irrelevant. However, the prestimulus certainty of a letter or number occurring in intratrial positions 2 and 4 was biased (67% and 100%, respectively). At positions 2 and 4 there was a difference in amplitude at the time of the stimulus for relevant and irrelevant stimuli. At intratrial position 4, where there was 100% certainty prior to the presentation of the stimulus, the amplitude at 0 msec was more negative when the stimulus was to be relevant than when it was to be irrelevant. This result is in agreement with the CNV literature in which a negative potential is found in anticipation of an "imperative" (relevant) stimulus. The results at the other electrode sites for this measure were similar (P3, O1, O2 not shown). Hemispheric differences were not prominent.

The other EP measures, amplitudes at 105 msec, 225 msec and 315 msec, showed major effects similar to those previously reported for midline electrodes (Chapman, 1973). Hemispheric differences were not pronounced. The measure which showed the most pronounced hemispheric differences was the amplitude at 315 msec (Fig. 4). The pattern of data at 315 msec suggests there may be differential hemispheric and brain area representation of various information processing conditions. The most obvious of these is a differential interaction of stimulus relevance and intratrial position with hemisphere ($F = 8.08$; $df = 3, 21$; $p < .01$). The question remains whether there is more differential representation of information processing in one hemisphere than in the other.

HEMISPHERIC DIFFERENCES IN DISCRIMINANT ANALYSIS

One way to assess whether responses from one area or another are more involved in various functions is by the use of discriminant analyses. If measures of responses from two (or more) brain areas are used to discriminate two (or more) experimental conditions, which measures do the best job?

Do EPs from the left (P3, O1) or right (P4, O2) hemisphere do a better job in discriminating various number/letter information processing conditions (relevant and irrelevant numbers and letters at four intratrial positions)? In the first application of the technique to be described there are sixteen classes to be discriminated from each other. To perform this discrimination, there are available five measures from each of four electrodes (twenty variates). The stepwise discriminant analysis (BMDP7M, Dixon, 1975)

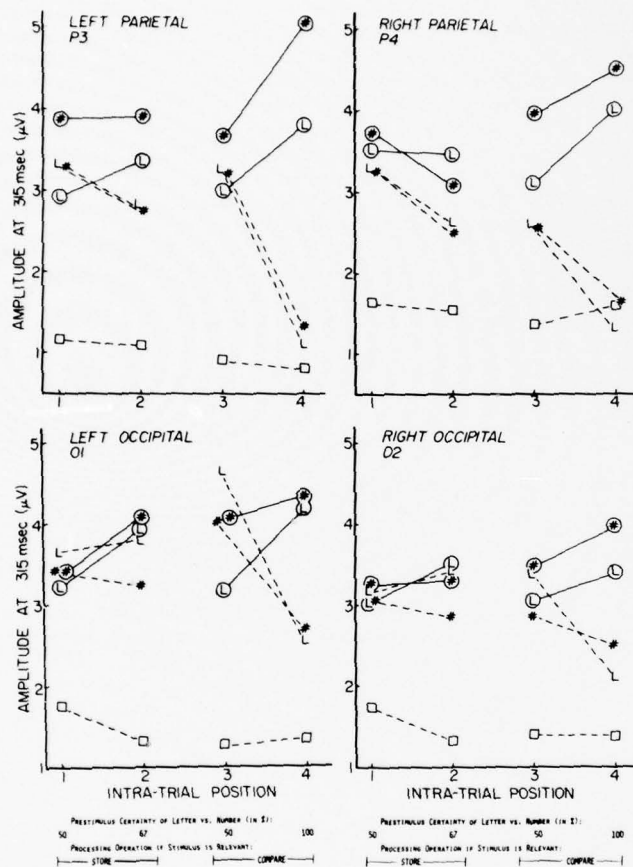


Fig. 4. Amplitude at 315 msec from left and right parietal and occipital electrodes for twenty experimental conditions. Measure is relative to EP level at time of stimulus. Other specifications as for Fig. 2.

selected the measures in the order of their effectiveness in classifying each of the 128 responses into the sixteen experimental conditions. The intercorrelations among the measures are taken into account. For the next measure to be added to the prediction equation the stepwise procedure selected the measure which is most

effective after the influence of the previously selected measures is taken into account. When the discriminant analysis is allowed access to all twenty measures, the single best measure in discriminating the sixteen information processing conditions was the mean amplitude over 480 msec from P3 (left parietal area). Of the first seven measures, six were from the left hemisphere (P3 mean over 480 msec, P3 at 0 msec, P3 at 315 msec, O1 at 315 msec, P4 mean over 480 msec, O1 at 105 msec, P3 at 105 msec, in order of their selection). Since there were 16 conditions to be discriminated, chance was $1/16$ or 6.25%. The development classification success using the first seven measures was 47.7%. A better index of the generality of the success rate is the jackknifed classification success which was 28.1% (Table 1). The jackknifed procedure is a cross-validation technique which assesses the classification success when each case is left out of the development set and then classified. This success rate is significantly better than chance (Chi square = 100.8; $df = 1$; $p < .001$).

Another assessment of hemispheric differences involves computing separate discriminant analyses with measures from each side alone and comparing the classification success rates. The results of this procedure also are given in Table 1. When discriminating the sixteen information processing conditions, the measures from the left side alone (P3, O1) achieved the same classification success as when measures from both left and right sides were available (28.1%). A lower classification success rate (20.3%) was obtained when measures from the right side alone (P4, O2) were used. These results indicate that measures from both left and right sides carry information about the information processing conditions, but that the left-side measures carry more such information than those from the right side. The fact that the left side alone does as well, or nearly as well, as when both sides could contribute to the classification equations indicates that the measures from the right side are largely redundant with those from the left side. The single most important variate of the ten available from each side was the mean amplitude over 480 msec from the parietal site (P3 for left side alone, P4 for right side alone).

Essentially the same pattern of results was obtained for additional groupings of the experimental conditions (Table 1). In order to provide comparisons which included the blank control flashes, the information processing design was simplified by ignoring whether the stimuli were letters or numbers. When discriminating the blanks and the resulting eight information processing conditions (relevant or irrelevant stimuli X 4 intratrial positions) the single best measure was again found to be the mean amplitude over 480 msec from P3. The first four measures selected for inclusion in the discrimination were from the left hemisphere. The final set of variables selected included five from the left and three from the right and accurately classified (jackknifed) 53.1% of the cases.

TABLE I

Discrimination of Experimental Conditions Using EP Measures
from Both Sides, Left Side, and Right Side

Groups	Chance	Both Sides	Left Side	Right Side
Information Processing				
16: number or letter	6.25%	28.1%	28.1%	20.3%
X relevant or irrelevant		(6L,1R)	(5P,30)	(3P,30)
X 4 intratrial positions				
Information Processing				
9: relevant or irrelevant	12.0%	53.1%	51.9%	46.9%
X 4 intratrial positions		(5L,3R)	(3P,20)	(5P,20)
and blanks				
Relevance				
3: relevant, irrelevant,	36.0%	85.0%	81.9%	76.9%
and blanks		(5L,3R)	(2P,20)	(5P,20)
Stimuli, physical				
3: numbers, letters,	36.0%	70.6%	71.2%	63.1%
and blanks		(6L,2R)	(4P,40)	(3P,30)
Individual Subjects				
8: subject	12.5%	96.9%	92.5%	94.4%
		(2L,8R)	(5P,50)	(5P,50)

Entries are jackknifed classification success rates (maximum for ten or less variates) from stepwise discriminant analyses (BMDP7M). All were significantly better than chance. The values of Chi square (1 df), corrected for discontinuity, ranged from 40.7 to 1033.7 ($p < .0001$). Below each percentage the number of left and right variates (L and R) or number of parietal and occipital variates (P and O) used in the classification functions are given in parentheses. The response measures were standardized separately for each of the subjects before performing the discriminant analyses except for the individual subject's analyses. Each subject's data for each measure were transformed to z scores with mean equal to 0 and stan. dev. equal to 1. This procedure has been found useful in reducing the effect of individual differences upon subsequent analyses which focus on the effect of experimental conditions (Chapman et al., 1978). The general conclusions reached with the subject-standardized measures are the same as those obtained with the raw measures; the main differences are improved rates of classification success when irrelevant subject differences have been removed.

Restricting selection of variates to the left side reduced the classification accuracy only slightly. Selecting variates only from the right produced a somewhat large reduction (Table 1).

Various kinds of functions may be assessed in a similar manner by using appropriate classification groups. For example, the side more related to stimulus relevance, regardless of stimulus or intratrial position, was assessed by discriminant analyses using three groups: relevant, irrelevant and blanks (Table 1). The results suggest that the left-side EPs carry more information concerning stimulus relevance (81.9%), but that right-side EPs also do a good job in discriminating relevance (76.9%).

Which side was more related to the different physical stimuli was assessed by discriminating three groups: number, letters and blanks (regardless of relevance or intratrial position). The results indicate that the variates from the left side are more related to differences among the visual stimuli (Table 1). The single most important variate was the amplitude at 315 msec from the left occipital area (O1).

It is possible to use this discriminant analysis technique to assess which is more related to individual differences. For this purpose the groups were the eight individual subjects. For these analyses the raw measures, before subject standardization, were used. Classification functions were computed which classified each EP case to one of the subjects, regardless of the experimental conditions (relevant and irrelevant number and letter, and blanks, in four intratrial positions). When measures from both sides were available, 96.9% of the EP cases were correctly classified to the individual subject by discriminant functions using two left variates and eight right variates. Measures from the left side alone did not do as well as measures from the right side alone (92.5% and 94.4%, respectively). This evidence suggests that the right side is more closely related to individual differences.

In general, the results indicate that measures over both hemispheres do a reasonably good job of discriminating various experimental conditions and individuals. The classification accuracy is well above chance in every instance. When discriminating information processing characteristics, variates from the left hemisphere are consistently selected first and often for inclusion in the discriminant equations. Although the differences are not statistically reliable, accuracy is consistently reduced when only variates from the right hemisphere are used in the discrimination. This consistency suggests that measures from the left side are more related to various information processing distinctions than measures from the right side. Measures from the right side appear to be more related to individual differences.

SUMMARY

In a number-letter information processing experiment, comparing laterally recorded EPs with each other and comparing the lateral EPs with previously reported midline EPs, the similarities are more striking than the differences. However, rather subtle hemispheric differences which are reasonably consistent have been found. The assessment of these lateral effects was facilitated by the use of control stimuli (blank flashes) and by particular kinds of multiple discriminant analyses. These have provided evidence that some kinds of processes are more strongly related to the left side while other processes are not. Information processing, including stimulus differences, was more discriminated by EP measures from the left side. Individual differences were more related to the right side.

ACKNOWLEDGEMENTS

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A SYSTEM TRANSFER FUNCTION FOR VISUAL EVOKED POTENTIALS

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INTRODUCTION

The electroencephalogram (EEG) and evoked potentials (EP) have long held the promise of being a way of studying the sensory processing of the brain. If we take the view that the EEG is a continuous output signal, some features of which represent the response to input signals consisting of sensory stimuli, we have an input/output system that seems suitable for application of engineering analysis techniques. Using this approach, Clynes et al. (1964) studied the brain wave responses to step, ramp and sine wave light stimuli. The step stimuli allowed them to obtain the transient response of the "system", and the sine wave stimuli allowed them to obtain the steady state response. These results, as well as the work of other investigators (Donker, 1975; Montagu, 1967; van der Tweel and Verduyn-Lunel, 1965), have demonstrated the nonlinear nature of steady state evoked potentials (SSEP). For stimulation by sine wave modulated light (SML) in the frequency range 5-9 Hz, a persistent second harmonic response is seen even at very low modulation depths. Further evidence of nonlinearity is seen in the poor results in attempting to predict the response to high flash rates based on superposition of responses from low flash rates.

In engineering analysis the transient response is usually characterized in the time domain by the impulse response, whereas the frequency domain is normally used to illustrate the steady state response via a transfer function. For a linear system the steady state frequency response can be obtained by the Laplace transform of the impulse response; thus either the transient or the steady state response is sufficient to characterize the system under investigation. However, in dealing with a nonlinear system the transient

response will usually not be sufficient to reveal the steady state response.

Recently several investigators have utilized Wiener's theory of nonlinear systems to develop identification technique for biological systems (French and Butz, 1973; Marmarelis and McCann, 1973; Marmarelis and Naka, 1974; McCann, 1974). This theory gives a description of a nonlinear system that is very general in nature. To call the description a transfer function is usually thought of as referring to frequency characteristics. However, the method does give a closed form function that relates the output to the input in the time domain.

Nonlinear analysis can also be employed when the input to a system is a point process and the output is a continuous signal. Krausz (1975) derived functional representations similar to Wiener for the case of a Poisson process input. This method has been applied to investigation of human somatosensory EEG responses (SER) to electric pulse stimulation (Scalabassi et al., 1977). The method has been termed "functional power series analysis" and involves the assumption that the nervous system operates as a stochastic transformation represented in a manner where the continuous output is an integral expansion of continuous kernels and a discrete input function. The kernels are analogous to Wiener's and have the same properties. This method applied to SERs has revealed that the nonlinear interactions noted may produce a facilitatory or an occlusive effect. These results have been useful in the study of multiple sclerosis.

The rest of this paper will give a brief introduction to nonlinear analysis methods and will show how they may be applied to human visual evoked responses to give a transfer function which relates the time waveform of a visual input stimulus to the evoked EEG output signal. Once this function is obtained it can be used to predict the transient and steady state responses to visual stimuli of similar form.

Along with these predictions we can also determine the nonlinear interaction present in the system as is usually obtained by recovery cycles from double pulse stimulation.

NONLINEAR SYSTEMS THEORY

Volterra series have been used to express the output of a nonlinear system with memory by an expansion of integrals of powers of the input (Bedrosian and Rice, 1971). Wiener recognized their usefulness in describing nonlinear circuits and developed an expansion that allows a system characterization similar to linear systems theory (Wiener, 1958).

Here the output is related to the input by a series of functionals:

$$y(t) = \sum_{n=0}^{\infty} G_n[h_n, x(t)]$$

We can view this system relationship as in the block diagram shown in Fig. 1.

The G_n are a complete set of orthogonal functionals. The first three are:

$$G_0[h_0, x(t)] = h_0$$

$$G_1[h_1, x(t)] = \int_0^{\infty} h_1(\tau) x(t-\tau) d\tau$$

$$G_2[h_2, x(t)] = \int_0^{\infty} \int_0^{\infty} h_2(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2 - P \int_0^{\infty} h_2(\tau, \tau) d\tau$$

P is the spectral density of a white Gaussian noise input.

The $\{h_n\}$ are the set of a Wiener kernels characterizing the system. They are essentially generalized impulse responses; G_1 is equivalent to the linear convolution integral and h_1 , the linear impulse response. The higher order kernels essentially describe the amount of nonlinear cross-talk in the system.

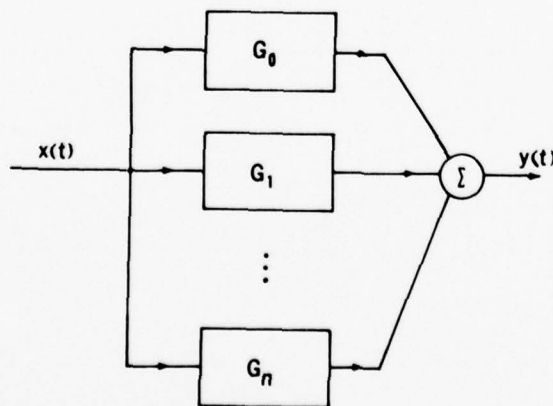


Fig. 1. System relationship of G functionals.

The system identification problem is now one of finding these kernels. Lee and Schetzen (1975) developed a cross-correlation technique where the general result is:

$$h_n(\sigma_1, \dots, \sigma_n) = \frac{1}{n!p^n} \cdot [y(t) - \sum_{m=0}^{n-1} G_m[h_m, x(t)]]x(t-\sigma_1)\dots x(t-\sigma_n)$$

This technique is based on a scheme of delays as shown in Fig. 2 for the second order case.

The actual digital solution is obtained by replacing the time averages by expected values which are estimated by discrete time correlograms. The continuous signals are replaced by their discrete time samples, and the kernels are represented by their values at discrete lag times.

Wiener showed that two nonlinear systems are equivalent if and only if their responses to the same white noise input is the same. This gives a method of testing how successful the system identification was by comparing the model response to the actual response. This comparison can be made by a mean square error measurement (MSE). Because the functionals of the system model are orthogonal, we know that if the series is truncated after the n th term (order) the result is still the best MSE approximation up to that term.

The theory is, in general, applicable to a wide range of physical systems. There are, however, several preliminary considerations

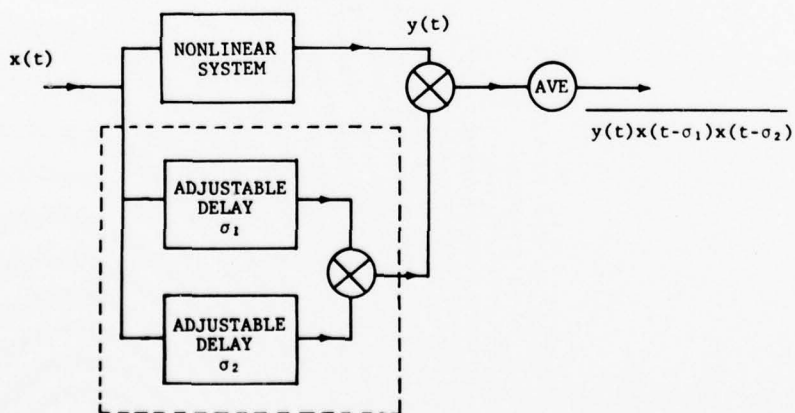


Fig. 2. Two dimensional delay used for system identification.

before attempting NL/TFA (Marmarelis and Naka, 1974). Two main requirements of a system are that it be time invariant and that it have a finite memory. If ergodicity cannot be assumed, solutions can still be worked by noting that for random processes the time average of the ensemble average is equal to the ensemble average of the time average (French and Butz, 1973). Since the system kernels are deterministic, the cross-correlations can be averaged across replications to give satisfactory results.

The finite memory consideration means that the system output must not depend on the infinite past in any significant way. For all physically realizable systems, this is obviously true. The problem is one of figuring how much of the past is necessary in order to determine the output to a desired degree of accuracy. Since the kernels can be computed only for a finite number of lags, this length should be chosen according to the system memory.

There are several parameters that must be determined in order to perform the identifying experiment: (1) bandwidth and dynamic range of stimulus; (2) length of experiment; (3) averaging or smoothing of input and output signals; (4) sampling rates. The order of the model depends on the nonlinearities present, and a second order model can, at most, account for second harmonic responses.

For a complete review of this type of nonlinear analysis see Hung and Stark (1977). Palm and Poggio (1977, 1978) give a rigorous discussion of some of the mathematical problems associated with the Wiener methods. They point out that since discrete time signals are used in actual practice, many of these difficulties are overcome.

METHODS

The length of the evoked EEG response to a light flash is on the order of 500 msec as found in standard average evoked potential studies. A reasonable starting point seems to be a model that would include the ability to predict such a response. With this in mind, a 20 sec stimulation period was chosen. This appears to be a good compromise between having enough length to compute a stable cross-correlogram and being short enough to have some assumption of stationarity of the subject's EEG.

It is clear that response averaging would be necessary to bring the signal-to-noise levels into the region where the analysis might be able to work. Starting with the assumption that at least as many trials as are necessary for normal AEP work would be required meant collecting about sixty trials. An actual trial consisted of 25 sec of white noise stimulation followed by a few seconds pause. The light level was left at the average level of the stimulus during the rest time in order to reduce problems with adaptation and ini-

tial eye blink transients. The last 20 sec of the EEG response was recorded for each trial.

Stimulus generation and control of data collection were provided by a PDP-11 computer based system for stimulus-response experiments. Gaussian noise was generated by averaging twelve values from a uniformly distributed random process and multiplying by a desired standard deviation. This procedure gives noise clipped at plus and minus 6 standard deviations. The Gaussian random numbers were then output at a fixed time rate to a digital-to-analog converter followed by a low pass filter to remove switching transients. Bandwidth was thus controlled by the rate of output, and dynamic range was controlled by the choice of standard deviation. A frequency range of 0-15 Hz was chosen with a mean stimulus intensity of 60 footlamberts. The standard deviation was set at a half log step of the mean value. The analog signal thus derived was used to drive an Iconix photostimulator which utilizes hot cathode fluorescent tubes. These tubes were set behind a rear projection screen of 43 X 55 cm placed at 50 cm from the subject's eyes.

Vertex and midline occipital leads referenced to right ear were recorded using gold disk electrodes. The EEG amplifiers used had a low frequency 3 dB point of 0.5 Hz. This was followed by an active low pass filter that was flat to 42 Hz and down 45 dB at 60 Hz. The filtered output was then converted to 10-bit digital values at a rate of 100 samples per second per channel. Each of the trials, as described above, consisted of the same white noise sequence. The responses were recorded on disk for later analysis.

RESULTS

Artifact-free trials were averaged together to give a 2000 point data record for both the vertex and occipital responses. Split half averages revealed very good agreement, indicating the validity of the response to this type of stimulus. The stimulus signal in log foot lamberts was sampled at the same rate to provide a 2000 point data record of the input signal. An example of the stimulus signal and response averages obtained is shown in Fig. 3.

An analysis program was written which performs the cross-correlogram computations. The program is set up to calculate the first and second order kernels and the model responses for each of them. It currently is running on a PDP-11/40 and has a limitation of 90 lags and 1000 data points. For an analysis with a model of 90 lags, using the first 1000 points of the vertex response, the resulting first order model response (G1), second order (G2) and the total model are shown in Fig. 3. The percent variance accounted for by the first order model is 16.5, and for the first and second

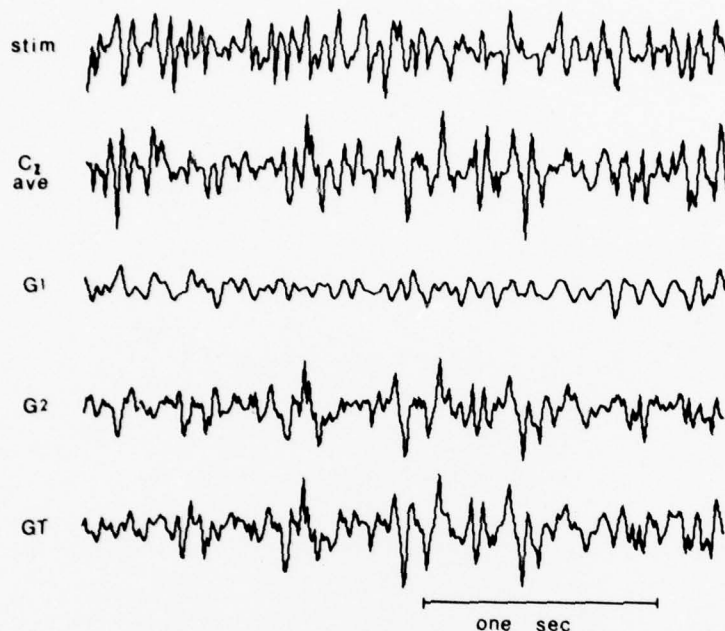


Fig. 3. Stimulus and response records with first and second order model responses.

order together it is 70. The visual agreement between the model's response and the actual response is seen to be quite good. Considerable nonlinearity is indicated since the percent variance accounted for statistics indicates that the major contribution to the model is from the second order (i.e., nonlinear) model.

The linear kernel (h_1) can be presented as a series of values at the discrete lag times they correspond to. The nonlinear second order kernel (h_2), however, is two-dimensional, and so a simple visual presentation is more difficult. The kernel may be thought of as consisting of two parts. The first is the diagonal values corresponding to equal lag times in each dimension. These represent the memory-less features of the nonlinearity. The off diagonal elements represent the nonlinear impulse interactions in time. These are the memory features of the nonlinearity. Fig. 4 shows the first order kernel and the main diagonal of the second order kernel.

The question arises as to whether the distribution of values in

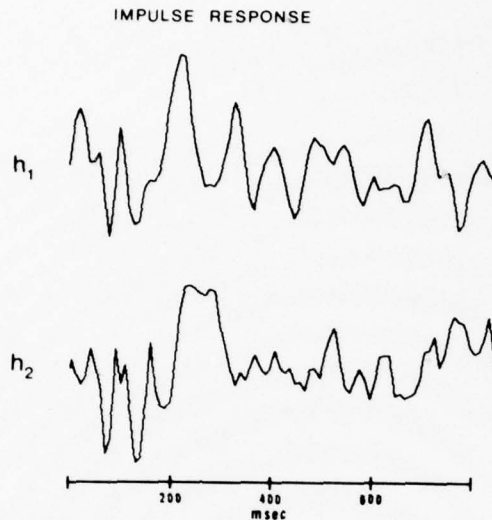


Fig. 4. First and second order kernel impulse responses.

the second order kernel reveals anything about essential features of the system under study. The form of h_2 for a memory-less nonlinearity followed or preceded by a linear system is easily computed (French and Wong, 1977). For a memory-less nonlinearity, such as a rectifier followed by a linear filter, the second order kernel has values only along the diagonal and exhibits no nonlinear interaction in time. This also indicates that such a system will still obey linear superposition.

For a linear system preceding a rectifier, the nonlinear kernel does have off-diagonal values. This form clearly gives an increase in nonlinear interaction times. Similar results are found if a general nonlinear kernel is considered to be preceded or followed by a linear filter. For a linear system following h_2 , the effect is to smear h_2 out along lines parallel to the diagonal. For the case of a preceding linear system, h_2 is spread out both parallel and perpendicular to the diagonal (Stark, 1968).

For the results here the major values of h_2 are seen to be along the diagonal with the most nonlinear interaction being contained within a relatively short period of time (i.e., close to the diagonal). A lot of smearing parallel to the diagonal is also noted. These indications would suggest that a short response system precedes the nonlinearity while a longer response time system follows it.

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Facilitation Effects of Nonlinear Interaction

The amount of off-diagonal activity in the second order kernel indicates the amount of nonlinear interaction present in the system. In order to more clearly quantify this interaction, a comparison of model responses, with and without nonlinear interaction, was undertaken. In EP work, recovery cycles are usually studied by looking at the effect of a preceding pulse spaced some variable length of time before another pulse. If nonlinear interaction is not present, the response to the second pulse will be a linear superposition of the responses to each pulse spaced appropriately in time. To simulate that situation, the diagonal only of the h2 response was used to

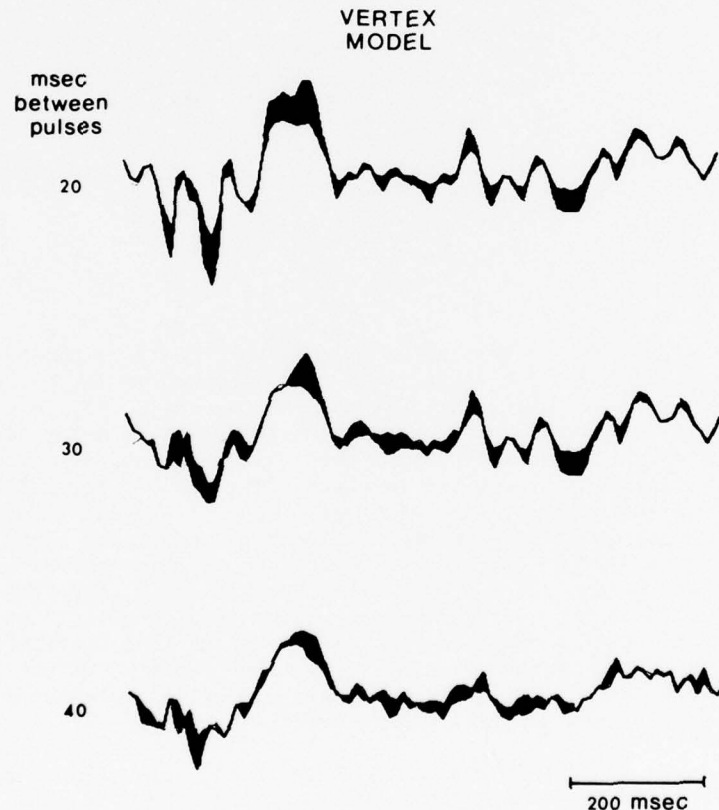


Fig. 5. Shaded area is the difference between responses to double pulses computed with and without nonlinear interaction.

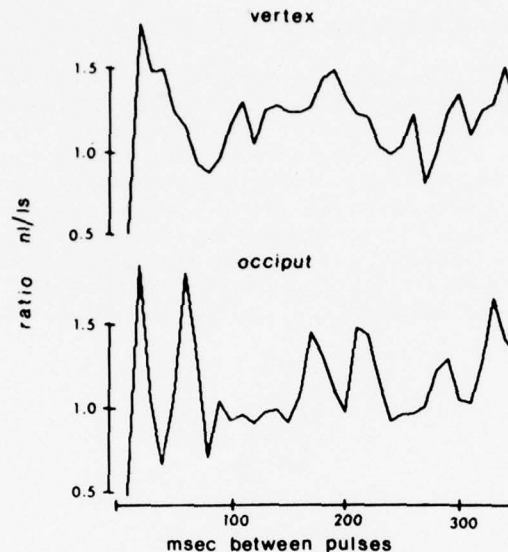


Fig. 6. Ratio of predicted responses to double pulses computed with and without nonlinear interaction.

compute an impulse response by superposition with the response to an impulse some delay before. This may be contrasted to the response to the second pulse using the full nonlinear kernel. Fig. 5 shows the results of this computation for several values of delay time between pulses. The major result of the interaction is seen to be an initial facilitation of the response. The action of a pulse 20 msec before another is to increase the size of the response considerably over what would be expected by linear superposition alone. These results may be quantified by comparing some measure of interest for each response. The maximum peak-to-peak value of the response within the first 350 msec was used in this case. The ratio of these measures for the two cases is plotted versus the time between pulses in Fig. 6. These curves are similar to those reported in the literature for SERs (Shagass, 1972). However, two pulse experiments using visual stimuli have not been widely carried out.

Although the difference in the form of the pulse response between the vertex and the occiput is clear, the form of the facilitation curve is similar. Both show an early peak and then a refractory period followed by an even response. As pointed out earlier, the spreading of the nonlinear kernel perpendicular to the diagonal

may be due to a linear filter preceding the nonlinear element. In this case that would suggest that an element common to both the vertex and occipital systems and early in the processing stage might be responsible for the nonlinear interaction. The usual source of the nonlinearity is considered to be rectification at the retinal ganglion level. If this is the case, the preceding linear element would indicate filtering at the retinal level. Thus caution is urged in attributing any recovery cycle effects to more central phenomena.

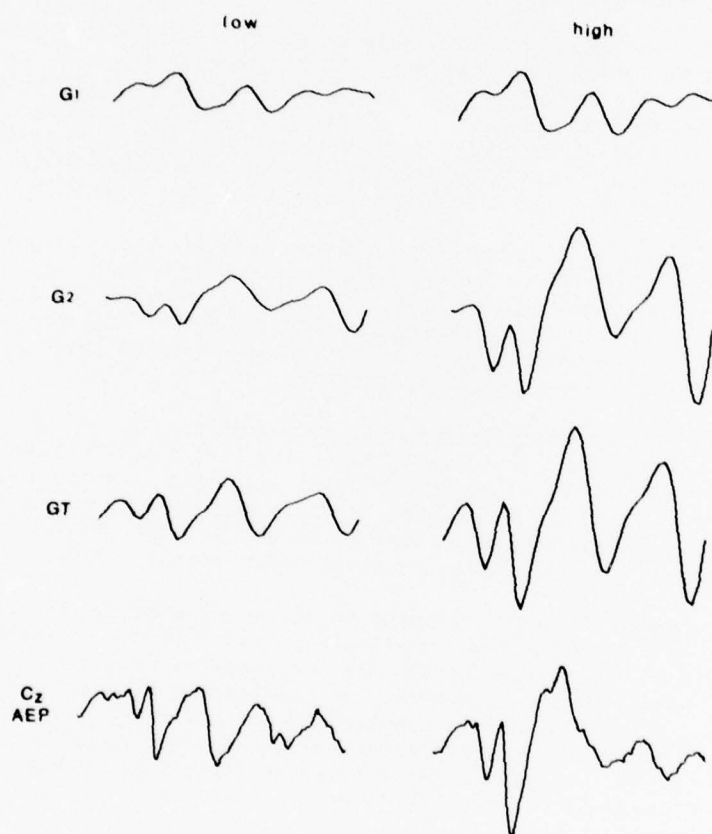


Fig. 7. Actual vertex AEP and the nonlinear model predicted response for a high and low intensity stimulus.

Prediction of the Transient Response

Vertex and occipital standard average evoked potentials were also collected using the same equipment. The EP experiment was one designed to study the relation of response measures to stimulus intensity (Buchsbbaum, 1978). Four intensities of light (3, 25, 80 and 220 footlamberts) were presented randomly intermixed but counter-balanced for preceding intensity. The individual stimulus was a half second light flash using the Iconix photostimulator. The EEG response for 512 msec after stimulus onset was averaged for sixty-four presentations of each intensity. Sampling rate was 250 Hz, giving 128 samples per average. A computer program was written to generate the transfer function model's response to similar transient stimuli. A half-second step function was used as the input signal, and the kernel outputs were computed.

When using different size step functions as input to the transfer function, it is seen that the relative contributions to the total response of the linear (G1) and nonlinear (G2) components are also different. This is shown in Fig. 7 for the vertex response. It can be seen that while the latencies of the peaks of the predicted response are quite similar to the actual AEP, the relative sizes of the peaks depend on the differential contributions from G1 and G2.

In looking at a sequence of AEPs to various intensity stimuli, similar shifts of peak size are noted (Buchsbbaum, 1978). The suggestion provided by this model is that some of this empirically noted variation may be due to differential stimulation of separate linear and nonlinear elements in the system. This result is quite similar to that for the model's predicted SSEPs.

More late activity is noted in the model's response than is usually seen in EPs. This may reflect the fact that the transfer function was arrived at by steady state stimulation which does not adequately follow the decay time of the actual response mechanisms. Some of the late activity is seen to be at the alpha frequency, suggesting again the interrelation of EPs with ongoing activity.

The model should be adjusted to allow for changing the relative sizes of the linear and the nonlinear portions of the response. This would allow closer study of whether the parallel system idea can account for changes in waveforms with increasing stimulus intensity. Further, a rigorous test is required to ascertain whether the model really reflects individual differences in waveform shape. This could be achieved by selecting subjects with reliable but clearly different AEPs and seeing if the transfer function identified for each subject is successful in reflecting this difference.

SUMMARY

This study develops a method of nonlinear transfer function analysis that is applicable to human EEG research. A white noise stimulation experiment that allows identification of the Wiener kernels of a nonlinear system is shown to be successful in modeling the human visual EEG system. Results, which are presented for both vertex and occipital EEG, show that over 70% of the response variance is accounted for. The resulting nonlinear transfer function is shown to be useful in studying several aspects of EEG. Nonlinear interaction in the model accounts for facilitation effects as seen in recovery cycle studies. Frequency response characteristics are also developed which suggest the existence of separate linear and nonlinear pathways in the visual system. Prediction of the transient response by the model is found to agree with actual AEPs to different intensities of stimulation. The resulting waveform appears to be a summation of differential contributions of linear and nonlinear components.

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SOMATOSENSORY EVOKED POTENTIALS IN MAN: MATURATION, COGNITIVE
PARAMETERS AND CLINICAL USES IN NEUROLOGICAL DISORDERS

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The cerebral somatosensory projection was the first to be mapped in primates and studied in intact man. While many publications have been dealing with the visual or auditory modalities (cf. Desmedt, 1977a,c) the somatosensory evoked potentials (SEP) have only recently become a topic for the many studies which elaborate on the earlier work (cf. Giblin, 1964; Debecker and Desmedt, 1964; Halliday, 1967). EPs are smaller and more localized on the scalp than the auditory or visual EPs. Furthermore the fast early components of the SEP have been distorted or missed in many studies that were done with inadequate amplifier bandpass or computer sampling rate (Desmedt et al., 1974). When these and other methodology problems are duly considered (Desmedt, 1977d), SEPs offer outstanding opportunities, namely because far field and primary cortical components, as well as later components, can be studied. Another feature is the remarkable length of the somatosensory pathway extending from peripheral nerves to spinal cord, brain stem and cortex which makes the SEP susceptible to a variety of pathological assaults that can be diagnostically explored by appropriate procedures. Finally SEPs recorded during perceptual decision tasks can differentiate cognition related changes involving either the early, middle range or later components in somatosensory perception (Desmedt et al., 1965; Desmedt and Robertson, 1977a,b; Desmedt, 1977e).

Normalization of SEP studies is only beginning. The SEPs recorded at the contralateral scalp over the postcentral gyrus comprise many subcomponents with diverse consistencies across subjects and with different significance. Many current ambiguities or contradictions appearing in the literature can be related to differences in control of various parameters. For example, the stimulus used to elicit SEPs is generally an electric shock to a mixed nerve

trunk. This technique is rather painful for the subject, and it has more limitations than currently believed because so many nerve fibers of different significance are simultaneously fired. It is wiser to restrict the input to the afferent fibers from a skin area by delivering the stimulus to fingers, toes or branches of sensory nerve (Desmedt, 1971). The SEP latency is affected by stimulus intensities in a range close to threshold (Desmedt et al., 1976). Intervals between stimuli in a series should preferably be random, and the mean frequency should not exceed 1/sec. When studying slow component waveforms the intervals should certainly exceed 4 sec to minimize sequential distortions and interactions (Desmedt and Debecker, 1972).

The EP components are conveniently identified by their polarity and peak latency (Donchin et al., 1977). Several factors affect the latency of the early SEP components. Any lowering of tissue temperature around the peripheral nerve increases the SEP latency since the afferent conduction velocity drops with a Q10 of 1.5 to 2.0 with temperature; it is, therefore, important to exclude this source of variation by checking local temperatures with a thermistor and by maintaining them at physiological range (Desmedt, 1971).

Another factor is the body size which influences the distance actually traveled from the stimulation point to the brain. For example, in normal adults the onset latencies of the first cortical event N22 of the SEP to finger stimulation varies from 15.5 to 22 ms

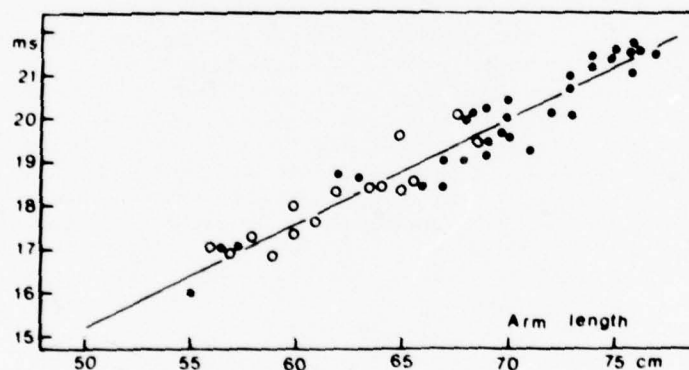


Fig. 1. Onset latencies (msec, ordinate) of N22 of the SEP to electric stimulation of fingers of the contralateral hand in normal adults, fifteen females (circles) and thirty-two males (dots). The abscissa represents the arm length in cm, as measured from the stimulating cathode to the shoulder (acromion bone) with the arm stretched. From J.E. Desmedt and E. Brunko, 1978.

in persons of body size from 1.5 to 2.0 m (Fig. 1). The peak latency of N22 can range from about 19 to 24 msec. For purposes of nomenclature, one can label the component from its actual peak latency in the subject (e.g., N21 or N23), or else use N22 throughout with the understanding that a variation of ± 3 msec can occur for different body builds (cf. Donchin et al., 1977; Desmedt and Brunko, 1978). The true significance of latency differences for early SEP components should be carefully considered when comparing subjects of different ages (Desmedt and Cheron, 1978) or clinical patients with nervous lesions.

It has not been appreciated that the electric stimulation of different skin areas elicits SEPs with genuinely different waveforms either in the normal adult (Desmedt and Brunko, 1978) or in the newborn (Desmedt, 1971). Fig. 2B shows the prominent early N24 cortical SEP component elicited by stimulation of the median nerve in a normal neonate during slow wave sleep. The N24 component presents similar features, but slightly longer duration, in the neonate during rapid eye movement sleep (Desmedt and Manil, 1970). This N24 is recorded over the postcentral cortex about 45 mm from the midline, but it is barely seen at the midline in A.

By contrast, stimulation of the posterior tibial nerve in the same session elicits an SEP with an early cortical positive component

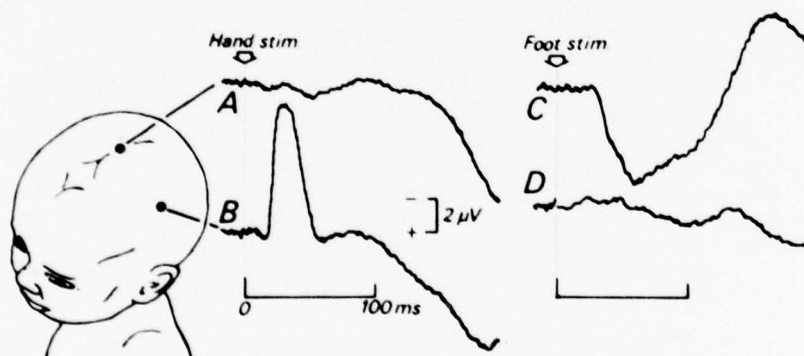


Fig. 2. Normal newborn of three days, slow wave sleep. Comparison of the early components of the SEP to stimulation of the right median nerve at the wrist (A,B) or of the right posterior tibial nerve at the ankle (C,D). The averaged SEPs are simultaneously recorded from two scalp locations shown on the left side. The reference is a mid-frontal electrode. Negativity of the active electrode registers upwards in all records. From J.E. Desmedt, 1971.

that is not preceded by a large negative component; this early SEP component to foot stimulation occurs close to the midline (C) but not at the more lateral scalp location (D). These and other recent results are in line with Penfield's cortical somatotopy in man. Extensive data on the profiles and scalp topography of cortical SEPs to stimulation of different skin areas can be found elsewhere (Desmedt and Brunko, 1978).

MATURATION

The SEP of newborns presents characteristic features related to the immaturity at birth of both the human brain and the afferent fibers of the somatosensory pathway. For example, the neonate SEP to finger stimulation presents a prominent cortical N30 which has a much slower time course than the corresponding N22 component in the adult. The mean onset latency of N30 in the newborn is 22 msec, and its mean duration is 15 msec during rapid eye movements sleeping or waking and 20 msec during slow wave sleep (Desmedt and Manil, 1970). The mean duration of the homologous N22 in the adult is 4 msec (Desmedt et al., 1976).

During maturation after birth, a gradual change of the N30 component occurs whereby the adult pattern is slowly acquired over a period of several years. Fig. 3A-C shows typical SEPs to finger stimulation at eight months. At this age, the large early negative component presents a rather short latency of 15 msec. For comparison the SEPs of two adults (Fig. 3D,E) present a latency close to the mean of 19 msec and an N22 of about 4 msec duration. Another major feature of SEP maturation depicted in these records is the increase of the subsequent positive P28 component. As discussed elsewhere, in relation to morphological data in immature mammals (Purpura et al., 1964), the prominence of the negative N30 at birth in man can be related to the precocious development of the superficial axo-dendritic thalamocortical synapses on cortical pyramidal neurones. The subsequent reduction in duration of the negative component together with the increase in size of P28 may, in part, reflect the later development of synapses on the basal dendrites of the cortical pyramids (cf. Desmedt, 1971; Desmedt et al., 1976).

Shortage of space does not allow a review of data about scalp topography of these and other SEP components, but it is already obvious that studies along these lines are uncovering unsuspected features of maturation of the human brain. For example, the question of the changes of onset latency of the early cortical negative SEP component with age raises several issues. The mean onset latency is 22.5 msec in newborns and 18.8 msec in adults, a highly significant difference ($p < 0.001$); however, the onset latency is much shorter, between 12.5 and 16.0 msec in children from about six

months to nine years (Desmedt et al., 1976). This somewhat surprising finding can be resolved if one takes into account the increase in length of the somatosensory pathway as the child grows. The body size of the twenty-nine subjects we studied is plotted in the lower part of Fig. 4. For roughly assessing the factor of pathway length, we divided the onset latency of N22 by the body size and found a highly consistent profile (Fig. 4, lower part, dots) which is fitted

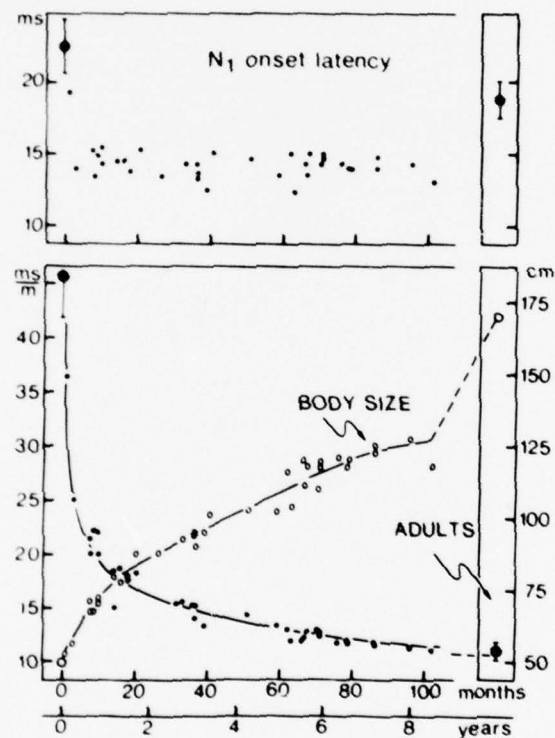


Fig. 4. The changes in onset latency of the early cortical negative component of the SEP with age (abscissa, months or years). Upper graph, onset latency in msec. Only the mean value with the standard deviation is indicated for the newborns and for the adults rectangle of the right. Lower graph, the body size of the same subjects in cm (ordinate on the right side; circles) and the onset latency of SEP divided by the body size (ordinate on the left side; dots). From Desmedt et al. (1976).

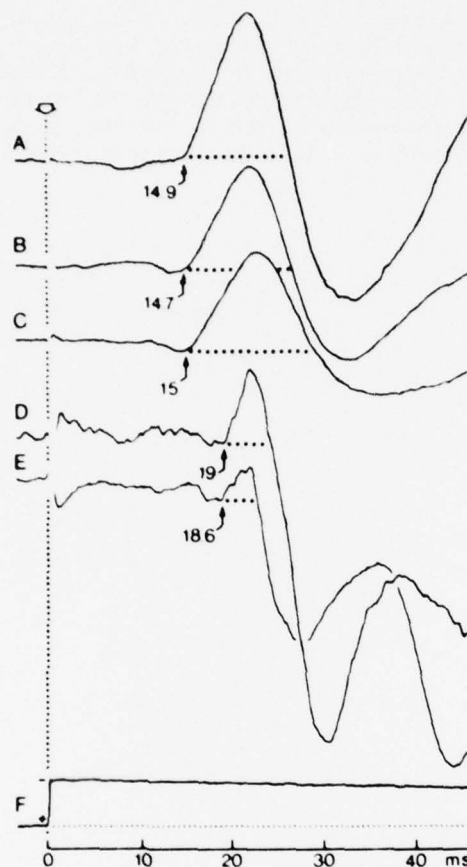


Fig. 3. Different SEP profiles in infants and in adults. SEPs elicited by stimulation of two fingers of the contralateral hand with brief pulses of 10 mA. A-C, female child of eight months and twenty-one days, 7.1 kg and 67 cm body size. A and C are different runs but same active recording electrode located over the postcentral gyrus 60 mm lateral to the midline. B is recorded with an electrode 50 mm from the midline. The three SEPs consistently show onset latencies and N22 duration characteristic for that age. D, SEP recorded in a normal male adult of twenty-seven years. E, SEP recorded in another male adult of thirty-six years. Finger stimuli delivered at random intervals with a minimum of 1 sec. Bandpass of the recording system 0.3 to 3000 Hz. All subjects awake with eyes open. F, calibrating step function of 0.5 μ V for A-C and of 1.25 μ V for D and E.

by a negative power function calculated as:

$$y = 32.44 \times x^{-0.221} \quad (r^2 = 0.962)$$

This procedure largely eliminates body size as a factor and depicts what is expected in an ideal population that would not grow and would remain at a constant body size of one meter (Desmedt et al., 1976). Then the onset latency of N22 would be 46 msec at birth (for a newborn of one meter body size) and 11 msec in the standard adult (also of one meter body size). The graph is helpful for focusing on true maturational features of the somatosensory pathway, once the effect of distance traveled by the afferent impulses is excluded. Thus it takes about eight years for a child to acquire adult conduction velocities (CV) along the entire somatosensory pathway. These data emphasize the remarkably slow maturation of somatosensory afferent conduction in man (Desmedt et al., 1976).

The above data dissociate pathway length and axonal maturation as factors determining the onset latency of SEP from birth to adulthood. A further study can provide more detail by recording the sensory nerve action potentials (cf. Dawson, 1956; Gilliatt, 1973). The maximum sensory CV estimated from the nerve potentials elicited by finger stimulation is much slower in newborns than in adults (Gamstorp and Shelburne, 1965; Desmedt et al., 1973) in agreement with the differences found for sensory axon diameters (Guthrecht and Dyck, 1970). In normal full-term newborns the sensory CV varies between 21 and 34 m/s and it rapidly increases to the adult range of 60 to 75 m/s in the 12-18 months after birth (Desmedt et al., 1973). This rather fast maturation rate of the peripheral sensory axons cannot account for the much slower changes in corticopetal conduction depicted in the lower graph of Fig. 4.

The problem can be clarified by plotting the progress of the peripheral sensory nerve volley and by extrapolating the calculated peripheral sensory CV to the segment between Erb's point and the dorsal column nuclei at the first cervical level (Fig. 5). The sensory nerve and Erb's point recordings provide consistent CV values of 67, 52 and 21 m/s in the subjects illustrated. The latency extrapolated for the DC nuclei, namely 15, 8 and 9 msec, is a little longer than the onset latency of the neck potential to finger stimulation. As previously suggested (Desmedt, 1971), it is then possible to divide the time interval to the onset of cortical SEP (corrected for three synaptic delays) by the measured distance from the base of the skull to the postcentral area in order to obtain an estimate of the "central" somatosensory CV; this gives 56, 21 and 7.5 m/s, respectively, for the adult, infant and newborn subjects in Fig. 5. Detailed results not reported here indicate that the maturation rate of the central somatosensory axons is, indeed, the major factor for the slow changes of onset latency of SEP as a function of age after

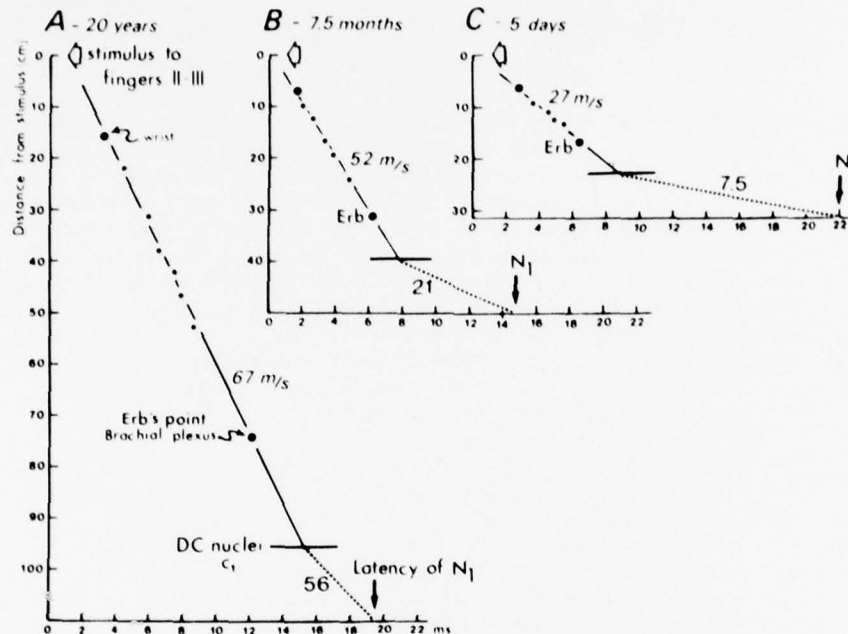


Fig. 5. Peripheral and central afferent conduction of a sensory volley elicited by stimulation of fingers II and III in an adult of twenty years (A), an infant of 7.5 months (B) and a newborn of five days (C). Abscissa, latency in msec of the earliest component recorded at peripheral nerve potential of cortical SEP. Ordinate, distance in cm traveled by the afferent volley from the fingers. The same scale is used for each subject to emphasize the different body sizes. The thicker dots correspond to the latency at the wrist or at Erb's point (supraclavicular fossa : brachial plexus). The peripheral afferent CV is extrapolated to the level of dorsal column nuclei. The dotted line corresponds to conduction from the DC nuclei to the postcentral cortex. The values proposed for the "central" conduction, namely 56, 21 and 7.5 m/s have been corrected for three delays. (From Desmedt et al., 1973.)

birth. This factor had not been disclosed until these evoked potential studies which raise important issues about the kinetics of maturation of the various pathways of the human brain (Desmedt et al., 1976). The method is relevant for clinical studies to identify peripheral versus central disorders.

COGNITION RELATED SEP COMPONENTS

It is known that the subject's attention to task stimuli influences the waveform of the corresponding evoked potentials. This parameter should never be ignored even when no specific task is given to the subject (as in standard clinical tests) because uncontrolled attention shifts introduce inconsistencies (cf. Donchin et al., 1977). The best known cognition related component is the P300, a positive wave of 250-500 msec peak latency elicited by task relevant signals which resolve the subject's uncertainty (Sutton et al., 1965; Desmedt et al., 1965; Vaughan and Ritter, 1970; Hilliard and Picton, 1978). The P300 can be elicited in purely somatosensory (thus intramodality) paradigms. For example, random sequences of near-threshold electrical stimuli are delivered to two fingers of each hand, and the subject is asked to pay attention and count the stimuli to one designated finger (target signals) in each run (Desmedt et al., 1977; Desmedt and Robertson, 1977a,b).

Fig. 6 shows positive components of about 400 msec peak latency in this case (this named P400) elicited by the target signals, no matter which of the four fingers is designated in any run (A1). The P400 does not appear in the SEPs to identical stimuli when these are not targets in the task and, therefore, remain largely ignored by the subject (B1).

When the random sequence of four finger stimuli is carried out at a faster pace (150/min instead of 40/min mean random rate), the identification by the subject of the target signals becomes quite difficult, and a new component occurs in the SEP. A negative wave with peak latency of 150 msec appears to target signals and also in the SEP to nontarget signals delivered to the adjacent finger of the same (attended) hand (Fig. 7). This N150 reflects a special cerebral processing that is required to distinguish the target and nontarget signals arriving from two very close skin areas. That the differentiation is efficient is, indeed, indicated by the score of the subject after each run; it is also interesting that a P400 component only appears in the SEP to target signals which suggests that the P400 may index completion of somatosensory target identification (Desmedt and Robertson, 1977a,b).

The next problem, whether primary EP components are influenced by the cognitive tasks, can be submitted to a critical test with the SEP in which the early cortical components of the postcentral projection are detected (this is not so readily achieved in auditory or visual modalities). Even when large enhancements of N150 or P400 occurred, the earlier N22 and P45 SEP components were not changed in the somatosensory paradigms at various rates and cognition-related changes started only after 55 msec (Desmedt and Robertson, 1977a,b). Thus, centrifugal gating at afferent relays (cf. Towe,

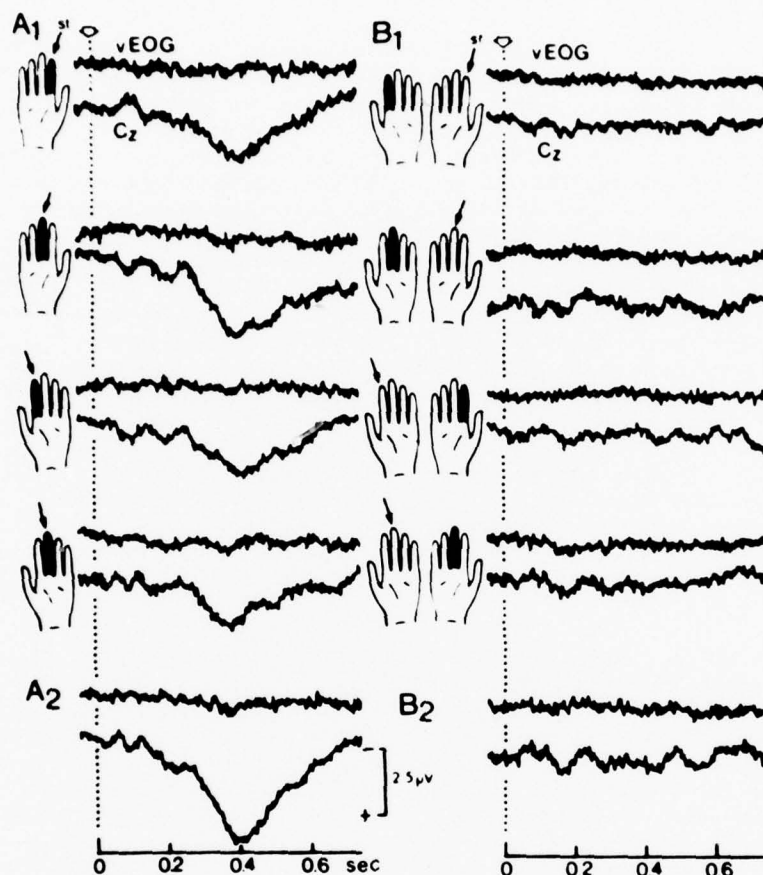


Fig. 6. The P400 component in intramodality selective attention. Random sequence of electrical stimuli 1 mA above subjective threshold delivered to four fingers. The hand figurines at the left of each pair of traces indicates in black the finger to which the subject is requested to pay attention in the corresponding run. The small arrows point to the finger stimulus that elicits the illustrated SEP. Active electrode at the vertex (Cz) with earlobe reference (lower trace of each pair). The upper trace is the vertical electro-oculogram (EOG) serving as check for lack of eye movement artifacts. A1, SEPs to target shocks shown for each of the four fingers (averages of seventy-five samples). A2, sum of these four averages (N=300). B1, SEPs to nontarget shocks delivered to the finger symmetrical to that attended in the opposite hand (N=75). B2, sum of the four averages for nontarget SEPs. The P400 appears only for the target signals. (From Desmedt et al., 1977).

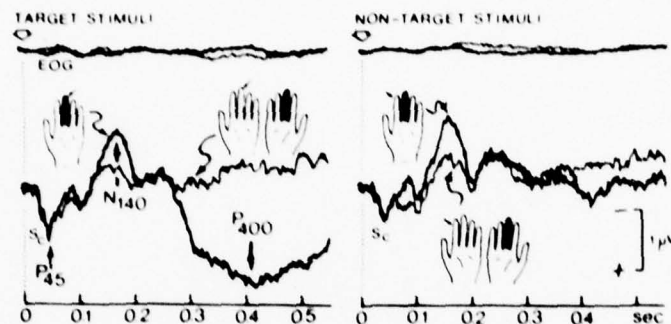


Fig. 7. The N150 and P400 components in intramodality selective attention task carried out at forced pace. Random sequence of electrical stimuli to four fingers. Two average SEP traces are superimposed for comparison, and they both are elicited by identical stimuli to the third (left side) or to the second (right side) finger of the left hand (small arrows). On the left, the third finger is designated as target for the task (thicker trace and black finger in figurines) and large N150 and P400 occur while the earlier P45 is not affected; the control thinner trace corresponds to runs in which the third finger of the opposite hand is the target. Notice that P45 is identical in both traces although N150 and P400 fail to appear in the thinner trace. Right side, nontarget stimuli to the second adjacent finger of the left hand in the same runs; there is virtually no P400, but a large N150 when the third finger of the left hand is a target in the task. The upper traces are EOG controls which exclude eye movement or muscle artifacts. (From Desmedt and Robertson, 1977.)

1973; Desmedt, 1975) is not a mechanism for these effects. However, the data leave it open whether delayed involvement of the powerful thalamocortical gating circuit of Skinner and Yingling (1977) might not participate in the switching on and off of the cognition-related SEP components. The above data must be taken into account when assessing SEP changes in neurological patients.

SEP USES IN PERIPHERAL NEUROLOGICAL DISORDERS

The conventional recording of sensory nerve potentials (Gillatt, 1973) is quite sensitive to nerve pathology, but it fails when the nerve potentials are markedly desynchronized. The cerebral SEP then provides a useful alternative because the cortex can achieve a time integration of the decimated and desynchronized afferent impulses (Desmedt et al., 1977; Desmedt, 1971).

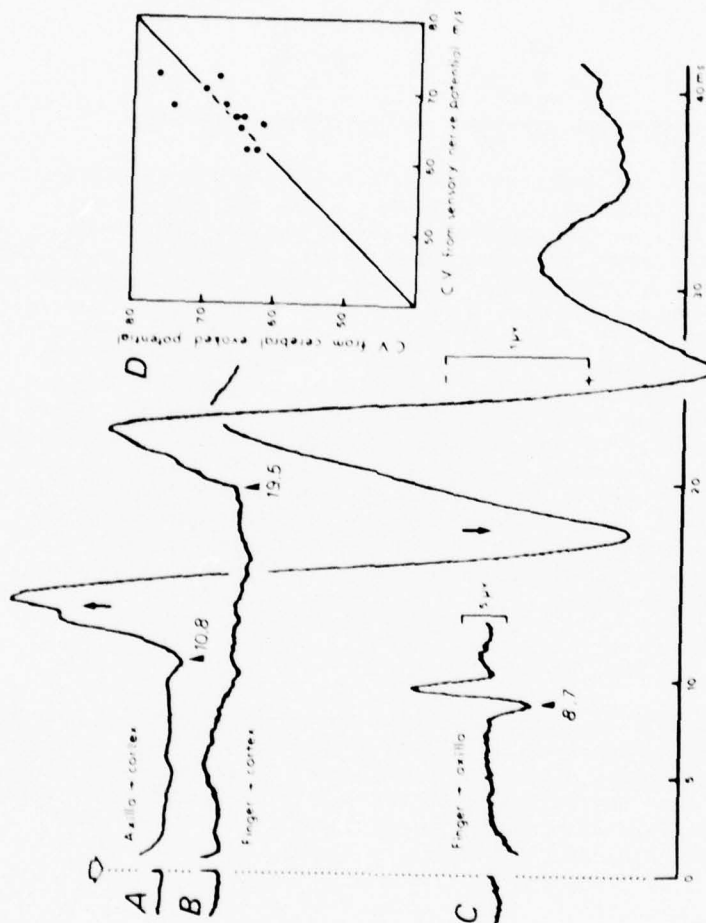


Fig. 8. Evaluation of the maximum afferent CV from the latency difference of SEP (ordinate in D) compared to the method based on recording sensory nerve potentials (abscissa in D) for eleven young normal adults. SEPs elicited by stimulation of the median nerve at the axilla (A) or of fingers II and III (B). Large N22 and P28 components are seen. The nerve potential (C) recorded from the median nerve at the axilla is elicited by the same finger stimulation. (From Desmedt and Noel, 1973).

Because the onset latency of the early cortical SEP component can be accurately estimated, latency differences are provided by SEPs to stimulation of fingers or nerves at different levels (Fig. 8). In normals the sensory CV calculated from SEP agrees well with that provided by direct sensory nerve potentials (Desmedt, 1971; Desmedt and Noel, 1973). The method used in lower limbs opens up useful diagnostic procedures since most common neuropathies involve predominantly the sensory fibers of the legs, and sensory nerve potentials are more difficult to record from these nerves (cf. Gilliatt, 1973; Shiozawa and Mavor, 1969; Desmedt and Noel, 1975). Fig. 9 shows the delays of the early cortical (positive) SEP to stimulation of the sural nerve at three levels which allows a sensory CV of about 50 m/s to be calculated. The diagram (Fig. 9D) depicts the effect of body size in twelve normal young adults for stimulation of the sural nerve at the lateral malleolus (Desmedt and Noel, 1975).

Clinical SEP data are documented elsewhere (Desmedt et al., 1966; Desmedt, 1971; Desmedt and Noel, 1973, 1975) and only one example is shown to illustrate the sensory CV evaluation from SEP in a patient with a section and suture of the median nerve at the wrist (Fig. 10). Five months after suture the SEP to distal finger III stimulation was very small, 0.3 μ V, and much delayed, 57 msec (Fig. 10B). The CV of the regenerating fibers was calculated as 5.4 m/s which agrees with animal data for newly regenerating axons. No nerve potentials could be recorded in this case.

SEPs provide unique diagnostic evidence in lesions involving the plexus or spinal roots, such as traction injuries or root compressions. For example, in a twenty-six year old patient with Stage III Hodgkin's disease, the delayed SEPs to femoral stimulation documented a bilateral invasion of the spinal roots by pathological tissue at the lumbar level (Desmedt and Noel, 1975).

SEP USES IN CENTRAL NEUROLOGICAL DISORDERS

There is current interest in searching for subclinical lesions of multiple sclerosis by averaging visual or auditory EPs (cf. Desmedt, 1977a,c) as well as SEPs (Desmedt and Noel, 1973; Matthews et al., 1974). These tests, in fact, can complement each other by exploring different brain areas, thereby increasing the potential yield of diagnostic findings at early stages of the disease. Peripheral CV is normal in multiple sclerosis (Desmedt and Noel, 1973), but the onset latency of SEP is frequently increased, especially for stimulation of limbs with a clinical sensory deficit (Fig. 11D). However, "silent lesions" with normal sensation and position sense in the stimulated area can be accompanied by significant increase of SEP latency (Fig. 11A,C).

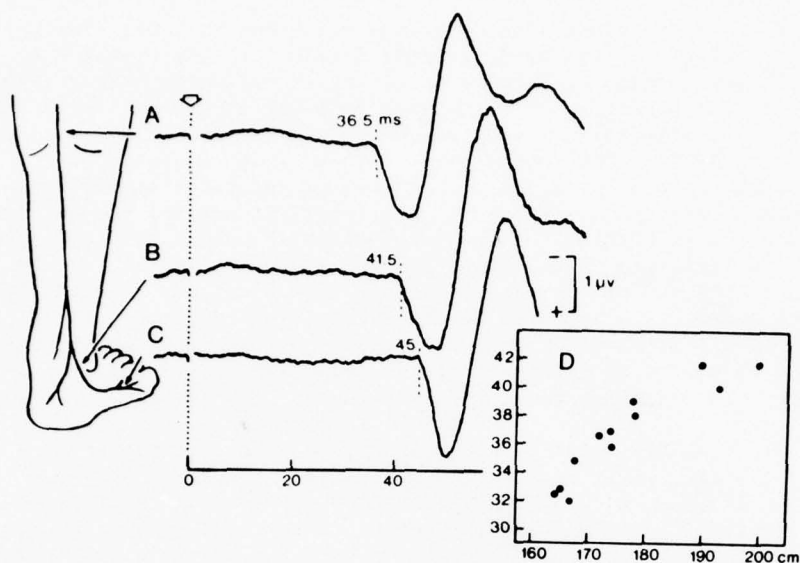


Fig. 9. Evaluation of maximum sensory CV in the sural nerve of normal young adults. SEPs recorded from the midline, 2 cm below Cz. Midfrontal reference. The SEPs start with a positive component (see above). The effect of body size is shown in D. (From Desmedt and Noel, 1975).

Another major SEP application is in vascular or tumor lesions of the brain stem. The afferent volley eliciting the cortical SEP travels in the dorsal column and median lemniscus pathway (Halliday, 1967; Desmedt, 1971). No changes of SEP are recorded in the Wallenberg syndrome in which the lateral vascular lesion spares the median lemniscus but involves the spinothalamic pathway (Halliday, 1967; Noel and Desmedt, 1975). In patients with a thalamic syndrome of Dejerine, the SEP has a reduced voltage and increased latency on the affected side (Tsumoto et al., 1973; Noel and Desmedt, 1975). In patients with a locked-in syndrome who present brain stem quadriplegia (infarction of basis ponti) and alert wakefulness, but who cannot communicate except to a limited extent by eye movements, the SEP is invaluable in documenting the extent of the lesion and the actual sensory loss. The median lemniscus in the ventral pontine tegmentum is in a critical position above the pontine infarct, and the SEP anomalies can document the dorsalward extension of the lesion



Fig. 10. Patient of thirty-seven years with a complete suture of the right median nerve at the wrist. Five months later no sensory nerve potentials could be recorded above the lesions site from the median nerve upon stimulation of the tip of the third finger. The patient described a faint subjective sensation when the third finger was tapped (Tinel sign). SEP recording from contralateral parietal scalp showed a much delayed and reduced potential (B). Notice the increased amplification for this trace. Controls are provided for the normal fifth finger (A) and for proximal third finger in the radial territory (C). (From Desmedt, 1971.)

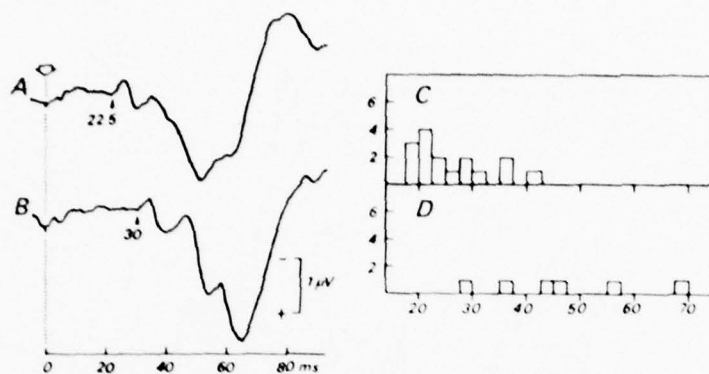


Fig. 11. SEP in multiple sclerosis. A, B female patient of thirty-four years with unilateral sensory deficit for finger position on the left side. SEP to stimulation of fingers II and III on the clinically silent right side (A) has a significantly increased latency for body size. The delay is larger for stimulation on the left side (B). C, D latencies of SEPs to finger stimulation in seventeen patients with multiple sclerosis. Clinical sensory deficits are absent in the patients in C and present in the patients in D. (From Desmedt and Noel, 1973.)

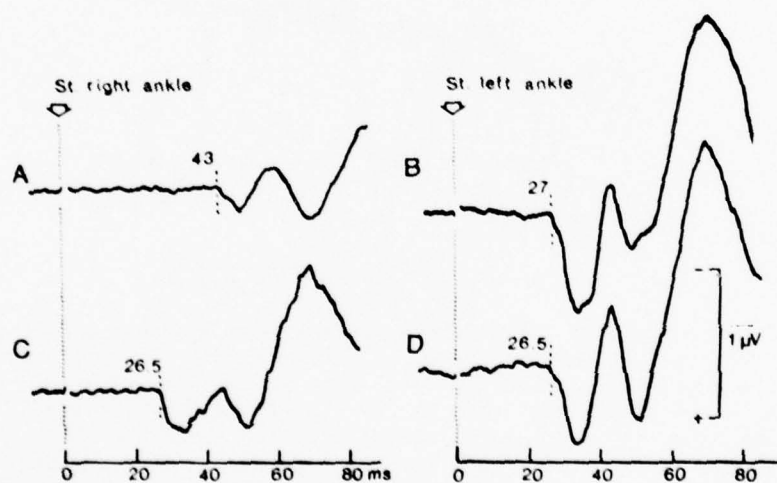


Fig. 12. SEPs to stimulation of the right (A,C) or left (B,D) posterior tibial nerve at the ankle in a female patient of twenty-five years with a locked-in syndrome studied either fourteen days (A,B) or twenty-two months (C,D) after the pontine infarct. The onset latencies of the early positive component are indicated. (From Noel and Desmedt, 1975.)

(Noel and Desmedt, 1975). For example, Fig. 12 shows the marked delay of the early positive SEP component to stimulation of the right (A), but not the left (B), posterior tibial nerve in such a patient. Twenty-two months later the SEP was still reduced but had acquired a fairly normal latency (Fig. 12C) while the control SEP for left stimulation (D) had not changed. These and other data about SEPs to upper or lower limb stimulation on both sides allow a fairly consistent mapping of the brain stem lesion.

SUMMARY

Somatosensory evoked potentials (SEPs) recorded from the intact scalp offer unusual possibilities for probing brain processes since both the early (primary) and late components can be identified in average records. The early cortical SEP component presents a latency that reflects primarily the conduction time from the peripheral stimulation site up to the parietal projection cortex. For example, the area of skin innervation which is stimulated influences both the waveform and scalp topography of the SEP. Between birth and adulthood the SEP feature presents dramatic changes, and the onset latency varies systematically in relation to both body growth and to maturation of the peripheral and central nerve fibers of the somatosensory pathway. SEPs elicited by stimulation of several fingers in random order at different mean rates have recently disclosed clear-cut changes during selective attention involving different designated fingers in different runs of the experiment. In such intramodality cognitive tasks, large P400 components appear only in the SEPs elicited by target signals. Earlier N150 SEP components are elicited at fast mean rates of the same task, and they can be seen both in the SEP to target and nontarget (adjacent finger) signals. Clinical uses of SEPs elicited by stimulation of appropriate areas in upper or lower limbs are documented for both peripheral nerve disorders and for the diagnosis of spinal, brain stem or cerebral lesions that involve the somatosensory pathway.

ACKNOWLEDGEMENTS

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EVENT RELATED POTENTIAL INVESTIGATIONS IN CHILDREN AT HIGH RISK
FOR SCHIZOPHRENIA

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INTRODUCTION

The search for the antecedents of schizophrenia has recently been advanced by the introduction of research in which individuals who are known to be at high statistical risk for schizophrenia are studied prospectively before the onset of disturbances in functioning (Pearson and Kley, 1957; Mednick and McNeill, 1968; Garmezy and Streitman, 1974; Erlenmeyer-Kimling, 1975). Children of schizophrenic parents are chosen as the high risk subjects; if one parent is schizophrenic, some ten to fifteen percent of the children are expected to develop the psychosis in adolescence or adulthood, and if both parents are schizophrenic, the risk increases 36-40 percent (Zerbin-Rudin, 1967; Erlenmeyer-Kimling, 1968; 1978). The high risk children are compared with children of normal parents for whom the risk estimate is only about one percent, on variables of interest to the investigating team, and, because the comparison is longitudinal, the development of the disorder can be followed. Thus, this research approach eliminates many of the biases prevalent when information is obtained from retrospective reports, although other types of problems may be inherent in the high risk design.

These relatively low risk estimates make it unlikely that large mean differences in any one variable will distinguish the groups. Thus, while group differences, if they occur, are important to examine, the investigator must search for deviant subjects whose scores could be heavily contributing to the differentiation of the groups. Even in the absence of group differences, this strategy should be followed if meaningful interpretation is desired.

The majority of hypotheses of how high risk children might perform and the tasks on which they are measured have come, naturally, from research with adult schizophrenics. However, because of the fact that adult schizophrenics are studied after the onset of the illness, it is often not clear whether what one finds is a premorbid characteristic or a consequence of the psychosis. The child at risk offers the researcher a way out of this dilemma, since it is possible to distinguish psychobiologic characteristics that are present before the onset of overt disturbances in functioning from those that appear later.

Event Related Potential (ERP) Studies in High Risk Samples

While autonomic indices have been used with high risk children for the past several years (Fein et al., 1975; Mednick and Schulsinger, 1973; Salzman and Klein, 1978; Venables, 1977), ERP techniques have only recently been utilized. If predisposition to schizophrenia is manifest in disorders of brain function, as many investigators believe, then scalp recorded ERP might be a useful tool in discriminating potential schizophrenics from both their normal control and nonvulnerable high risk counterparts.

Saletu et al. (1975) reported finding no amplitude differences, but did find shorter latency peaks to repetitive auditory stimuli in their high risk group. They concluded that their data supported the hypothesis, consistent with the GSR findings of Mednick and Schulsinger (1973), that the potential schizophrenic, like his adult counterpart, is characterized by a state of hyperarousal. However, their statistical methodology and ERP measurement techniques detract from the forcefulness of this conclusion. We (Friedman et al., 1978b) studied the auditory evoked potentials (AEP) elicited by repetitive tones in twenty high risk and twenty normal control children. Analyses of between groups differences yielded no significant findings. We were, however, able to identify subgroups of both the high risk and normal control samples that differed significantly from each other. In contrast to the findings of Saletu et al. (1975), the high risk subgroup had longer latency P190 and P400 components than the normal control subgroup. No significant amplitude differences were found, although there was a trend for the high risk outliers to have larger amplitude ERP.

In the above studies, there was no task imposed upon the subject, and thus latency shifts could be due to disturbances in either sensory or cognitive information processing. Herman et al. (1977) reported finding no group performance differences but longer latency and larger amplitude N100-P200 responses in their high risk

sample in response to signal and nonsignal stimuli in a version of the continuous performance test. They concluded that this reflected a maturational lag in visual information processing. Herman et al. (1977) recorded between Cz and Oz which could have reduced their chances of seeing large amplitude late positive components, as well as obscured any between group topographic differences.

Potentials recorded from children in a well defined psychological task requiring sustained attention, in which components can be related to stages of information processing and topographic data are available to aid in the interpretation of component behavior, should prove more fruitful in the study of high risk children, especially in view of the frequently reported cognitive dysfunctions in adult schizophrenics. The data to be reported here are from a preliminary analysis of the ERP of high risk (HR) and normal control (NC) children who are part of a longitudinal high risk study (Erlenmeyer-Kimling, 1970). These children are measured on a variety of psychological, biological, psychophysiological and sociological variables. The psychophysiological battery consists of the measurement of autonomic functioning during two threshold procedures, ERP recording during a combination "odd-ball" and missing stimulus paradigm, and during two versions of the continuous performance test (CPT). Previous versions of the CPT have been shown to differentiate adult schizophrenics from other psychiatric samples, as well as HR from NC children (Kornetsky and Orsack, 1978; Ruchmann et al., 1977; Grunebaum et al., 1974). It is the data from the CPT tasks that are the subject of this paper.

METHODS

Subject Selection

The "at risk" children were obtained through their parents in a screening of consecutive admissions at six psychiatric hospitals in the greater New York area between June, 1971 and December, 1972. In order to be included in the study, the patients had to be white, English speaking, married at the time of admission and still living with the spouse, and have two or more children between the ages of seven and twelve. The hospital records of patients meeting these criteria were independently evaluated for schizophrenia by two senior psychiatrists and a resident at New York State Psychiatric Institute without knowledge of the hospital diagnoses or the medications prescribed. No family was taken for study without a unanimous diagnosis of schizophrenia in the patient.

NC children were obtained through the cooperation of the Nassau and Rockland County School systems. Parental criteria for inclusion were the same as those for the HR sample, with the exception that any child who had a parent with a history of psychiatric hospitalization was eliminated from the study.

Laboratory Procedures

The first time they were seen, the children were given a large battery of psychologic, psychophysiologic, psychiatric and neurologic tests. The visual ERP procedure which is the subject of this report was not given until the third round of testing (1977-1978) some six to seven years later. This is a preliminary analysis performed on the data of roughly one-third of this cohort of subjects, some of whom are still being seen in our laboratory. In all aspects of the testing procedure, the experimenters were blind with respect to whether a child was HR or NC.

CPT Tasks and EEG Recording Procedures

The tasks used were modifications of the CPT originally described by Orzack and Kornetsky (1966). Our current versions of these tasks have been fully described elsewhere (Friedman et al., 1978c), and only a brief description will be given here. In Task A, the subject had to respond to the number 08, which occurred fifteen times per block, and withhold his response to any other number (45 per block); in Task B, the subject had to respond to the repetition of any immediately preceding number, which occurred sixteen times per block, and withhold his response to numbers that did not repeat (48 per block). The signal to nonsignal ratio was 1:4 in each task. Fifty msec duration stimuli were flashed at moderate intensity with an ISI of 1 sec. Task B imposed greater processing demands than Task A in that subjects had to sequentially store and compare successive non-signals as potential targets, whereas in Task A the target stimulus was pre-determined and each trial required a simple match or mismatch decision. Eight blocks of stimuli were delivered for each task, with tasks alternated two blocks at a time. The subject was instructed to respond as quickly as possible with a fingerlift which activated a reaction time (RT) key. RTs greater than 1200 msec were considered misses.

EEG was recorded from a midline montage at Fz, Cz, Pz and Oz, and vertical EOG was recorded from above the right eye with a reference electrode on the right earlobe. Data were recorded on a Beckman Dynograph Type RM recorder, amplified 20,000 times with a time constant of 1 sec and high frequency cutoff at 30 Hz, and were stored along with RT on digital tape. Data acquisition and

stimulus presentation were controlled by a PDP 11/10 computer which digitized the EEG at 4 msec intervals for a period of 1000 msec (100 pre- and 900 post-stimulus). Averages of signal and non-signal stimuli were computed across blocks. There was a total of 120 signals and 360 nonsignals for Task A, and 128 signals and 384 nonsignals for Task B, but removal of extracerebral artifacts attenuated these numbers in most subjects.

The data of the first 60 HR and NC children seen for this round of testing were selected for preliminary analysis. These subjects were divided into age bands of 11-13, 14-15 and 16-18. Table I presents the characteristics of the two groups. As can be seen, age and sex are well balanced between the groups. #SM and #SF refer to the number of children of schizophrenic mothers and fathers respectively. #Both refers to the number of children whose parents were both diagnosed as schizophrenic and #Mixed refers to the number of children in which one parent was schizophrenic and the other was diagnosed as psychotic depressive.

TABLE I: CHARACTERISTICS OF THE HIGH RISK AND NORMAL CONTROL GROUPS

	Mean Age	#Males	#Females	#SM	#SF	#Both	#Mixed
11-13							
HR	12.6	5	2	4	2	0	1
NC	12.5	5	6				
14-15							
HR	14.5	6	5	7	2	2	0
NC	14.5	7	2				
16-18							
HR	16.8	7	5	9	1	0	2
NC	16.8	6	4				
TOTALS							
HR	14.6	18	12	20	5	2	3
NC	14.6	18	12				

ERP Measurements

Because of the complex nature of the waveforms elicited during these tasks (Friedman et al., 1978c) and the need for objective, quantitative ERP indices in evaluating abnormalities in ERP morphology and topography, principal components factor analysis (PCA), factoring the covariance matrix, was employed. This method allows us to associate factors with specific ERP components that are affected by the experimental variables and affords objective confirmation of components we have visually identified in the grand mean and individual data (see also Squires et al., 1977). Since the factors are extracted due to their association with experimental variance (cf., Donchin and Heffley, 1978; Glaser and Ruchkin, 1976), abnormalities in waveform morphology can be directly related to the experimental variables. We use the factor scores as the baseline to peak measures.

To determine if the group factor structures were the same, this analysis was done separately for the HR and NC groups. The data base for each analysis was an 83 time point (at 12 msec per point) by 480 waveform data matrix (30 subjects by two tasks by two stimuli by four electrode sites). Six factors were varimax rotated using the BMDP4M computer program (Dixon, 1975).

RESULTS AND DISCUSSION

Figure 1 presents the grand mean data averaged across the 30 subjects in each group by task and stimulus. The waveforms from both tasks consisted of a complex of positive waves which appear to differ for the two tasks, and, to some extent, for the two groups. The visual evoked potential (VEP), clearly visible at Oz, consisted of a positive-negative-positive complex, consistent in latency and amplitude across tasks and stimuli. N150 appears to be more negative to the Task B waveforms. In order of increasing latency, the remaining positive peaks are: (a) P240, maximal at Cz, present to both stimuli of both tasks. (b) P350, maximal at Pz, clearly seen in the nonsignal waveforms of each task. (c) As RT increases, the signal waveforms become increasingly differentiated, so that P350 can be seen in the Task B signal, but is not discernible in the Task A signal. This peak appears to be larger to the nonsignals of Task B. (d) P450, with a parietal focus, is seen in the ERP of both stimuli in both tasks, with much larger amplitude to signals than nonsignals, and of larger amplitude to the nonsignals of Task B than those of Task A. (e) P550 is seen most clearly in the Task B nonsignals, and is not visible at all in the Task A nonsignals.

The vertical lines mark mean RT, which was significantly longer in Task B than in Task A ($p < .0001$). In general, the HR group shows

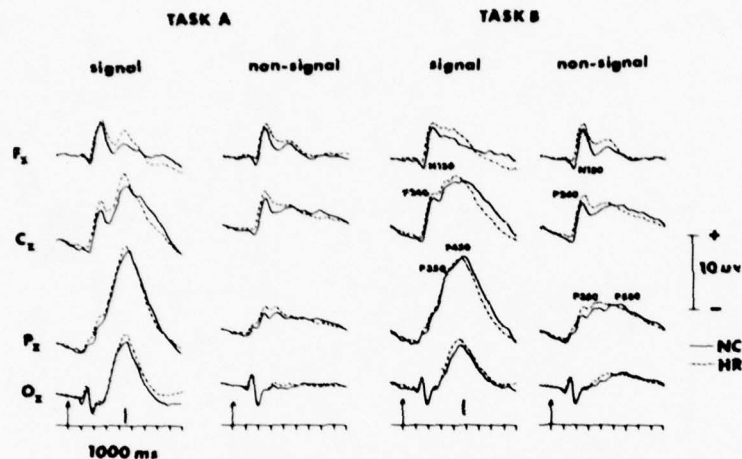


Figure 1. Grand mean ERP recorded from 30 HR and 30 NC children in response to the stimuli from both tasks at the four electrode sites.

more frontal activity in the P240-P450 region, less initial negativity (N150) and a faster return to baseline following the late positive complex (LPC) than do the NC. The HR group shows somewhat less very late positive activity, especially in response to the nonsignals of Task B.

Principal Components Analysis

Figure 2 presents the loading functions after varimax rotation for both groups of subjects. It is clear that the shapes of these functions are identical, with the main difference occurring in their latencies, which are approximately 50 msec longer to peak for the HR group for factors 3 through 6. With the exception of Factor 2, each loading function is associated with a component seen in the grand mean: Factor 1 with P450, Factor 3 with P240, Factor 4 with P550, Factor 5 with P350 and Factor 6 with the increasing negativity preceding the stimulus and culminating frontally in N150. Factor 2 has large positive loadings at a point in time when P450 is decrementing, and appears to represent return to baseline following this late positive activity.

At the present time, we are beginning to explore the sources of latency variance which are evident in the factor loading functions. Our method has been to systematically reduce the data set

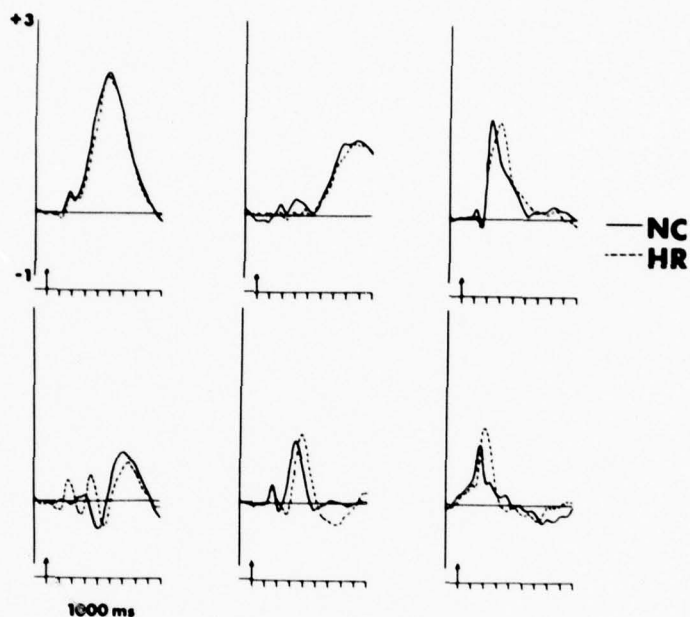


Figure 2. Rotated factor loading functions resulting from PCAs performed separately for each group across tasks, stimuli and electrodes.

of performing PCA for each group separately by task demonstrated replication of the factor structures seen when the analysis was done across tasks, and demonstrated that the longer latency N150, P240 and P350 factors seen for the HR group occurred within the Task A waveforms only. We are now attempting to further pinpoint the source of these latency shifts by performing PCA separately for type of stimulus within a task. The results should tell us whether the source is in the signal, nonsignal or both.

Factor Score Analyses

Repeated measures ANOVA were used to assess the effect of risk group, age group, task, stimulus and electrode location on the factor scores resulting from a PCA pooling the data from both groups of subjects. All findings reported below are significant at the .05 level or better, unless noted. All factors showed

topographies extremely similar to the ERP components with which they were associated. Consistent with the increased processing demands of Task B, the waveforms of this task were marked by significantly greater P350 and P550 amplitude factors, with a large effect on P450 amplitude elicited by nonsignals of Task B. The P550 component appears independent of the P450 component, which is larger to signals than nonsignals, since it behaves differently, being larger to nonsignals and has a more posterior distribution, especially in the Task B waveforms. It appears similar in latency and distribution to the P4 component recently reported by Stuss and Picton (1978). P240 appears to be a visual P2, and as such, its greater amplitude in the Task B waveforms can be attributed to the greater attentional requirements of this task, since others have shown that P2 is affected by attentional demands (e.g., Picton and Hillyard, 1974; Friedman et al., 1973). This factor showed a trend towards greater amplitude in the HR group ($p < .09$). Consistent with the greater attentional requirements of Task B is the finding of more initial negativity (N150 factor) in this task than in Task A. This factor was less negative in the brain potentials of the HR group, but this did not attain statistical significance ($p < .07$). Both CNV and N100 have been shown to be greater under conditions requiring greater attentiveness (Hillyard et al., 1973; Picton and Hillyard, 1974; Friedman et al., 1973; Tecce, 1972). The baseline factor, which appears similar in topography and temporal relationship to the LPC to the slow wave factor of Squires et al. (1977), behaves differently. Their slow wave was affected by probability. Our baseline factor was larger to nonsignals, the frequent stimulus, than to signals, the infrequent stimulus. The HR group produced faster returns to baseline than the NC group, as did the oldest group of subjects compared to the younger subjects.

The current data confirm our previous findings (Friedman et al., 1978c) and those of others (e.g. Squires et al., 1975; Adam and Collins, 1978; Stuss and Picton, 1978; Thatcher, 1977; Keselica et al., 1977) in demonstrating multiple positivities within the latency range of P300, and their greater amplitude elicited by Task B (Friedman et al., 1978a).

Identification of Deviant Subjects

Because not all children with a schizophrenic parent are genetically at risk, it is necessary to search, within the HR sample, for a subgroup of individuals whose deviance on selected measures suggests that they are the vulnerable members of the group. To begin with, we assessed the effects of the variables of stimulus, task and electrode locus on the factor scores obtained from separate PCAs performed for each group, using repeated measures ANOVA. Despite the differences in the peak latencies of the factors be-

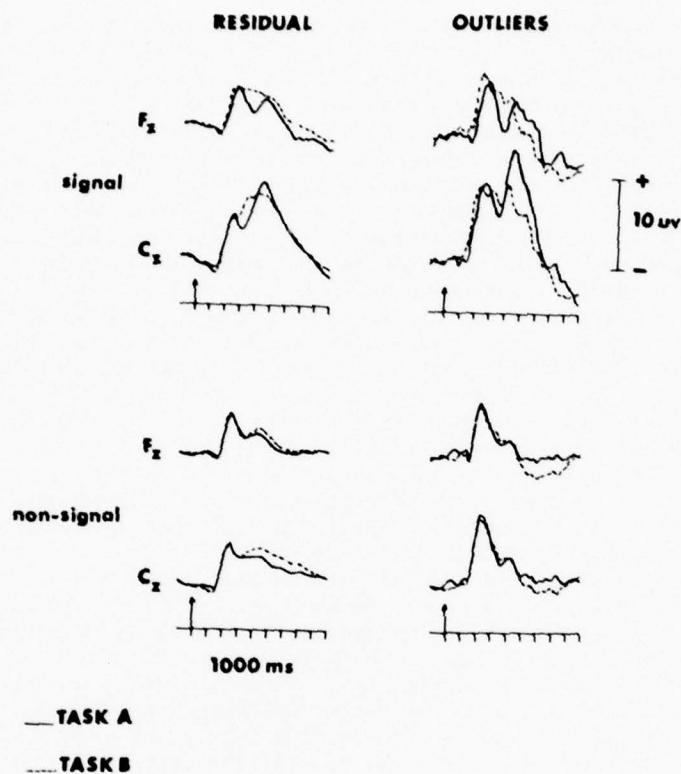


Figure 3. Grand mean ERP averaged across the four outliers and across the remaining 26 HR subjects (Residual) in response to both stimuli from each task.

tween groups, these factors behaved similarly in each group, supporting the conclusion that these factors were the same. The fact that they behaved similarly for both groups allowed us to use the NC factor score coefficients to compute factor scores for the HR group. Theoretically, this method should produce more deviant HR than NC subjects. The distribution of factor scores for each factor was inspected, and, using a criterion of a score of ± 2 , subjects were chosen as outliers, and the number of subjects outlying on one or more factors was tabulated. There were ten HR and two NC that were outliers on four or more factors, and this difference was highly significant ($\chi^2=6.12$, $p<.02$). Within this group, four subjects, all of whom were HR, showed a consistent pattern of factor scores: large-amplitude frontal P450 to signal stimuli; large-

amplitude P240 activity to both stimuli and tasks; little initial negativity; the absence of very late positive activity and faster returns to baseline. The ERP at Fz and Cz where these effects were greatest, averaged across the four subjects, are shown in Figure 3. Also shown is the residual HR grand mean (N=26) after these four subjects were subtracted. Note that the outliers' LPC to nonsignals is not well defined and is of smaller amplitude than the residual mean. The outliers do not show a difference in LPC amplitude between the nonsignals of the two tasks, which is clearly seen in the residual mean, nor do they show a difference in initial negativity between tasks, a result which is also prominent in the residual mean.

Relationship to Adult Schizophrenic Waveforms

In reviewing the adult schizophrenia ERP literature, Buchsbaum (1977), Roth (1977) and Shagass (1976) concluded that consistent features of the adult schizophrenic's waveform were: large amplitude components prior to 100 msec, reduced amplitude LPCs, low amplitude CNV and a tendency towards reduced N100-P200 amplitude. The outliers demonstrate large amplitude P240 components, but this peak is later than those reported to be of large amplitude in adult schizophrenics. However, the outliers do show low amplitude LPCs to nonsignals of both tasks, which might be indicative of deficient information processing or a difference in the way in which they analyze the relevant information from the two tasks. The absence of very late positive activity (P550) adds strength to this hypothesis. Stuss and Picton (1978) and Thatcher (1977) have reported a late positive wave, which they have labelled P4, which has a timing and topography similar to our P550, and which Stuss and Picton (1978) have related to the processing of feedback information in a learning task. The absence of this component in the outlier waveforms might be indicative of a failure to use this information and to make perceptual adjustments while performing the task. The reduced negativity seen in these subjects, and the lack of difference in this factor between tasks, could reflect a failure to differentially direct attention between tasks, each of which appears to require a different level of sustained attention.

CONCLUSIONS

The major similarities between the outliers' waveforms and the morphology most often reported for the adult schizophrenic was seen in low amplitude LPC and early negativity to nonsignals and reduced negativity to signals. Marked differences were also noted: these subjects exhibited large amplitude P240 components to all stimuli and large amplitude LPCs to signals. Inasmuch as

the various ERP components reflect different aspects of information processing, it is to be anticipated that each component will have differential importance as an index of potential psychopathology. It is also likely that the child at risk who eventually manifests schizophrenia may show a different premorbid ERP response pattern than the adult schizophrenic. It will only be upon follow-up of these individuals that one should be able to detect ERP characteristics that are true premorbid indicators and those that are a consequence of mental dysfunction.

Our strategy is to follow those children whose ERP waveforms are found to be deviant to determine whether they will also be identified as outliers by other components of our psychophysiological and psychologic test batteries. One of the outliers reported here was also an outlier on an auditory evoked potential measure of deviance during an earlier round of testing (Friedman et al., 1978b), and three of the four current outliers were also deviant on attentional measures given during the first round of testing (Erlenmeyer-Kimling et al., 1978). However, not all of the children seen during the first two rounds of testing have been seen for the third round, and any conclusions regarding overlap on measures of deviance would be premature at this time. This analysis of our data serves to point up our more cognitively oriented approach to ERP research with HR children and to outline our methods for determining which children might be the most vulnerable. Inherent in this methodology is the fact that even if a small number of children are chosen on this basis, it will not be until several years later, at an age when onset is expected, that validation of the selection process will occur.

SUMMARY

Visual ERP were recorded from thirty children at high risk for schizophrenia (HR) and from thirty normal controls (NC) during two versions of a continuous performance test which differed in their task demands. Task A required a simple target identification, while Task B, the more complex of the two, required comparison of successive stimuli. Multiple late positive components were seen in the brain potentials of both groups of subjects in both tasks. Principal components analysis (PCA) confirmed the existence of these components, yielding identical factor structures for both groups of subjects. Late positive components were generally of larger amplitude in the Task B waveforms, while N150 and P240 factor amplitudes appeared to be influenced more by the difference in attentional requirements between the tasks. There was a tendency for N150 to be less negative and P240 of larger amplitude in the HR than in the NC group. Four children at high risk for schizophrenia were selected on the basis of extremely deviant factor

scores. Their brain potentials were characterized by low amplitude N150, small LPCs to nonsignal stimuli, large LPCs to signal stimuli and high amplitude P240 components. While differences between their pattern of response and those of the adult schizophrenic were seen, similarities were also evident. Those components which were deviant in these HR children have also been shown to differ from normal in the adult schizophrenic and are components that have been implicated in mechanisms of selective attention and cognitive processing.

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LATE POSITIVE COMPONENT (LPC) AND CNV DURING PROCESSING OF
LINGUISTIC INFORMATION

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INTRODUCTION

The late positive component of the evoked potential (LPC) and the contingent negative variation (CNV) have been investigated with visual and acoustic stimuli by many researchers studying linguistic processing. CNVs were investigated during word category discrimination by Burian et al. (1972). LPCs were studied during information processing in sentences by Friedman et al. (1975) and during semantic information processing of words by Thatcher and April (1976). Different lateralization for noun- and verb-evoked EEG scalp potential fields was reported by Brown and Lehmann (1977). Both Burian and Thatcher tried to apply ERPs evoked by words in testing aphasic patients. We studied CNV and LPC during processing of linguistic information to find out if ERPs can be useful for testing the recognition of Japanese sentences and words.

METHODS

I. Examination of Sentence Recognition

The experimental subjects included three healthy right-handed persons, three aphasics and one person with auditory agnosia. Three meaningful sentences and three meaningless sentences (which were composed by exchanging the predicates of the three meaningful sentences with one another) were used as acoustical or visual stimuli. Each sentence comprised five spoken syllables or four visually presented characters (two Kanji and two Kana). The subject

was able to determine whether the sentence had a meaning or not by understanding the key information (the fourth syllable or the third character) in the acoustically or visually presented sentence.

The acoustically presented sentences were delivered by a simple, random aural-stimulator (Goto et al., 1976) which consisted of a conventional 4-channel tape recorder, an endless tape, a control signal detector, a memory, an analog switch and a motor drive controller. With this stimulator, the examiner could choose one of either three meaningful or three meaningless sentences for reproduction through monaural headphones with exact timing (100 msec monosyllable voice, 900 msec interval). One second after the last word of the meaningless sentence a red lamp, placed 130 cm in front of the subject, was lit as the imperative stimulus for the CNV task.

The 9 X 9 or 11 X 11 red light emitting diode (LED) matrix, viewed binocularly, was used to present sequentially each character in the visual sentences (40 msec character, 960 msec interval). One second after the last word of the meaningful sentence, nine LEDs in the center of the matrix were lit as the imperative stimulus for the CNV task. The LED matrix subtended a visual angle of 2° .

The three meaningful and three meaningless sentences were presented in a random sequence with approximately the same number of occurrences of each sentence. The subject, lying comfortably in a supine position, had been told previously that each meaningful sentence was followed by a sign, and he was ordered to press a switch as fast as possible after the task signal.

The recording electrodes were placed at C3 and C4. The reference electrodes were placed at the ipsilateral mastoid processes. A ground electrode was placed on the forehead. EEGs were amplified using 3.0 second time constant amplifiers, stored on a data recorder and analyzed using an electronic averager. EOG artifacts were checked.

II. Examination of Word Recognition

Seven right-handed, healthy subjects and three slightly impaired aphasics served in the experiments. The 11 X 11 red LED matrix was used as the visual stimulator similar to the sentence examinations (Fig. 1). Since the ability of Japanese aphasics to use Kanji and Kana can be selectively impaired, we examined LPCs during information processing in semantic match and mismatch between either two successive Kanji or two successive Kana words presented in Thatcher's paradigm (Thatcher and April, 1976).

In the Kanji experiments a series of visual displays (20 msec



Fig. 1. Kanji, Kana and random dot pattern presented on 11 X 11 LED matrix.

stimulus duration, 1 stimulus/sec) were presented. A given trial comprised, sequentially, a variable number (two to six) of random dot displays (RDDs), then a first Kanji, then another variable number (two to six) of RDDs, then a second Kanji, then two RDDs (Fig. 2). Ninety to 120 trials were presented. The second Kanji was the same, antonymous or semantically unrelated to the first Kanji. Five pairs each of identical, antonymous and semantically neutral single Kanji words were used as the two successive Kanji words (Table 1). The subjects were told to press one switch as fast as possible after a trial with semantic match, and another key for mismatch between two successive Kanji. The recording electrodes were placed at T3, T4, T5, T6, P3 and P4. The linked ears served as a reference. A ground electrode was placed on the forehead. The ERPs were averaged separately for semantic match and mismatch cases. EOG artifacts were checked.

In the experiments of Kana words, each Kanji or one RDD in the above mentioned trial was replaced by three sequential Kanas or RDDs of 30 msec in duration with 80 msec intervals (Fig. 3). Eight pairs

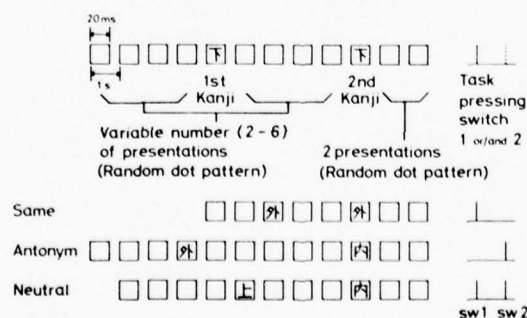


Fig. 2. Trial sequences in Kanji experiment.

Table 1. First and second Kanji pairings. S: same; A: antonymous; N: semantically neutral.

1st Kanji	2nd Kanji	
明 (light)	上 (up)	(N)
上 (up)	下 (down)	(A)
暗 (dark)	上 (up)	(N)
暗 (dark)	暗 (dark)	(S)
下 (down)	下 (down)	(S)
外 (out)	外 (out)	(S)
下 (down)	上 (up)	(A)
内 (in)	外 (out)	(A)
下 (down)	明 (light)	(N)
外 (out)	内 (in)	(A)
外 (out)	下 (down)	(N)
内 (in)	内 (in)	(S)
明 (light)	明 (light)	(S)
明 (light)	暗 (dark)	(A)
上 (up)	内 (in)	(N)

each of equal, antonymous and semantically neutral Kana words were used as the two successive Kana words (Table 2). Tasks for semantic match and mismatch between two successive words, EEG recording and data processing were the same as in the Kanji experiments.

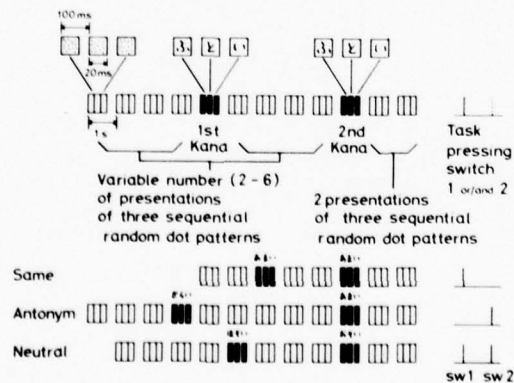


Fig. 3. Trial sequences in Kana-words experiment.

Table 2. First and second Kana-word pairings. S: same; A: antonymous; N: semantically neutral.

1st Kana	2nd Kana	
おもい (heavy)	あまい (sweet)	N
たかい (high)	ひくい (low)	A
よわい (weak)	ひろい (wide)	N
ふとい (thick)	ふとい (thick)	S
ひくい (low)	ひくい (low)	S
かるい (light)	おもい (heavy)	A
あまい (sweet)	あまい (sweet)	S
せまい (narrow)	ひろい (wide)	A
ふかい (deep)	あさい (shallow)	A
はげい (thin)	おそい (slow)	N
からい (salty)	あまい (sweet)	A
たかい (high)	よわい (weak)	N
ひろい (wide)	ひろい (wide)	S
はげい (thin)	ふとい (thick)	A
かるい (light)	かるい (light)	S
あさい (shallow)	はやい (quick)	N
おそい (slow)	からい (salty)	N
つよい (strong)	よわい (weak)	A
ふかい (deep)	ふかい (deep)	S
はやい (quick)	はやい (quick)	S
はやい (quick)	おそい (slow)	A
からい (salty)	あさい (shallow)	N
つよい (strong)	つよい (strong)	S
せまい (narrow)	たかい (high)	N

RESULTS

I. Sentence Recognition

Healthy subjects. In the experiments with acoustic stimulation, evoked potentials were obtained to each spoken syllable. The amplitude of the N1 component of the evoked potential to the first syllable was the largest. The amplitudes of P300 to the first and the fourth syllables were larger than those to the others. In the experiments with visual stimulation, the amplitude of N1 to each character was small. P200 was observed for every character. The amplitudes of P300 to the first and the third characters were much larger than those to the second and the fourth characters. P300 latency to the third character was longer than any of the other P300 latencies. P650 to the first and the third characters tended to appear, but were not observed in responses to the second and the fourth characters (Fig. 4). In both acoustic and visual experiments,



Fig. 4. Visual evoked responses to each character in a sentence. (*)=P300; (**) =P650.

CNV began to develop at the first information (the first syllable or character) and continued until the subject pressed the switch in response to the meaningful sentences. However, when the subject was stimulated by the meaningless sentences, a CNV began to develop at the first information, continued until the key information was given (the fourth voice or the third character) and then disappeared (Fig. 5, Fig. 6).

In the examination of the aphasic patients, confused responses were observed in sentence differentiation. Confused responses to the acoustically presented sentences were observed in 0-40% of the aphasic patients in comparison with 0-4% of the healthy subjects. The confused responses to the visually presented sentences were observed in 0-68% of the aphasic patients in comparison with 0% of the healthy subjects. The evoked potential components N1 and P300 were observed, but the CNV amplitudes were very small or at zero level in the aphasic patients. There was no difference between the CNVs produced by the meaningful and meaningless sentences (Fig. 7).

In the investigation of the auditory agnostic patient, the evoked potential N1, P300 and CNV were not observed when the patient was stimulated with the acoustically presented sentences (Fig. 8). But N1, P300 and CNV were very similar to those in healthy subjects during visual sentence stimulation (Fig. 9).

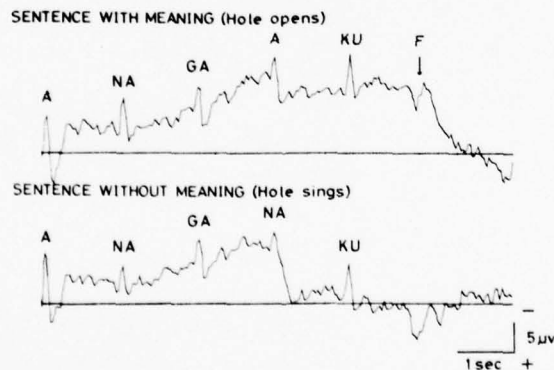


Fig. 5. Evoked potentials and CNV obtained by aural sentence stimulation. F: flash; Top record: CNV accompanied by stimulation of meaningful sentence; Bottom record: CNV accompanied by stimulation of meaningless sentence.

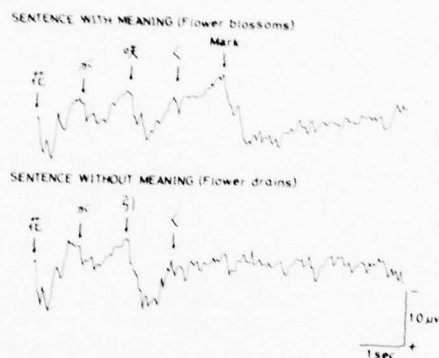


Fig. 6. Evoked potentials and CNV obtained by visual sentence stimulation. Top record: CNV accompanied by stimulation of meaningful sentence; Bottom record: CNV accompanied by stimulation of meaningless sentence.

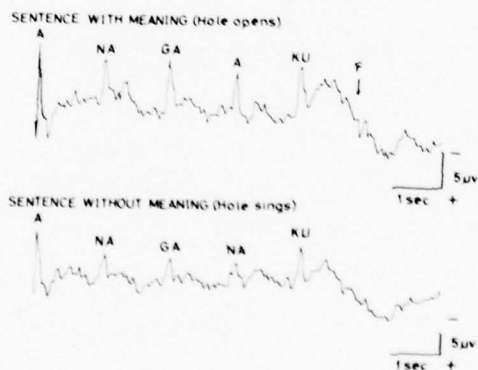


Fig. 7. Evoked potentials and CNV obtained by auditory sentence stimulation in an aphasic patient.

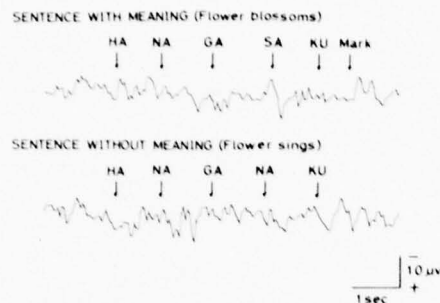


Fig. 8. Evoked potentials N1, P300 and CNV were not observed in the auditory sentence stimulation experiment in an auditory agnostic patient.

II. Word Recognition

Healthy subjects. In the Kanji word experiments, in temporal leads N1 amplitudes to the second Kanji were not marked, but P200, P300 and P650 to the second Kanji were observed. The amplitudes of P300 and P650 in right side derivations were larger than those in left side derivations (Fig. 10). N1, P200 and P300 to the first Kanji were similar to those to the second Kanji, but P650 to the first Kanji was not marked. In the evoked responses to the RDD just before and after the second Kanji, N1 amplitudes were not marked. P200 was observed, but neither P300 nor P650 appeared.

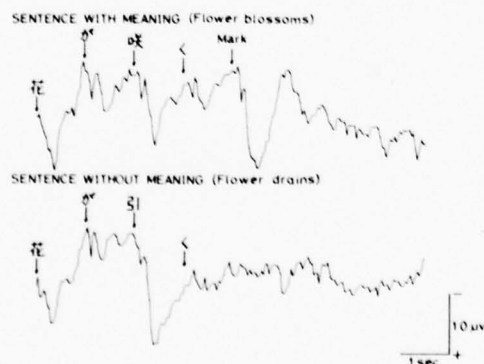


Fig. 9. Evoked potentials and CNV observed in the visual sentence stimulation experiment in an auditory agnostic patient.

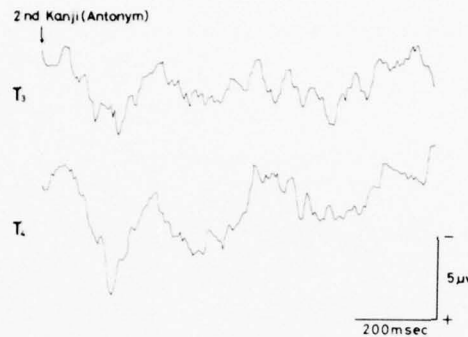


Fig. 10. Evoked response to the second Kanji (antonymous).

Latencies of P200 to these RDDs were shorter than those of P200 to the second Kanji (Fig. 11). In the Kana word experiments, N1 amplitudes to the second Kana words were not marked, but P300 and P650 were observed. P300 amplitudes to the second Kana words in right-sided derivations were larger than those in left-sided derivations (Fig. 12). N1, P300 and P650 to the first Kana words were similar to those to the second Kana words, but not marked. In the evoked responses to three sequential RDDs just before and after the second Kana words, P300 was observed, but P650 was not observed (Fig. 13). Evoked responses at P3 and P4 were similar to those at T3, T4, T5 and T6.

In the examination of aphasics confused responses were frequently observed in recognition tests of Kanji and Kana. In

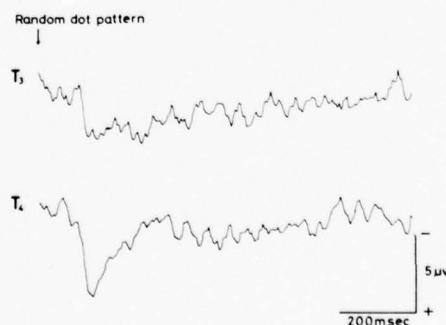


Fig. 11. Evoked response to random dot pattern (just before the second Kanji).

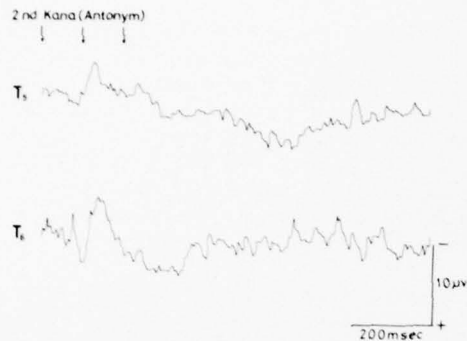


Fig. 12. Evoked response to the second Kana-word (antonymous).

slightly impaired aphasic patients evoked responses to the second Kanji tended to be similar to those observed in healthy subjects, but the amplitudes of P300 and P650 were smaller. Peak latencies of P300 and P650 in aphasic patients were much longer than those in healthy subjects.

DISCUSSION

Friedman et al. (1975), in a study of averaged visual evoked potentials to sequentially flashed words comprising sentences of two conditions, reported that P300 latencies to words which delivered information (last or second word according to condition) were longer than P300 latencies to any of the other words in the sentence. In our experiment with visually presented sentences, P300

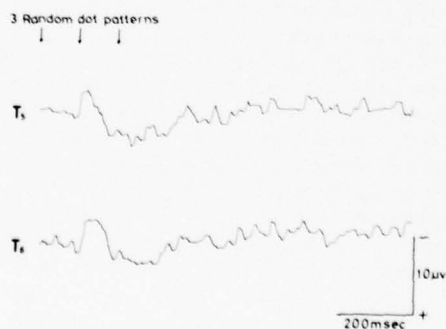


Fig. 13. Evoked response to three sequential random dot patterns (just before the second Kana-word).

latency to the key (third) character was longer than that to the other characters. This result is compatible with the result obtained by Friedman's group. They observed the presence of CNVs in some circumstances but not in others. In our experiments a difference between CNVs produced by meaningful and meaningless sentences was observed whenever the subjects discriminated the sentences. When the subjects could not discriminate the sentence, recognition response in the CNV was not observed, and CNV amplitudes were small or zero.

Burian et al. (1972), using two different word groups as warning and non-warning stimuli and following only one group with a flash, argued that the appearance of the CNV following only one group was positive, objective proof that the subjects understood the test words. In our experiments, using not word groups but sentence groups, such a difference between CNVs was observed in the healthy subjects. The recognition response in CNV was not observed in the examination of the aphasic patients who could not discriminate the sentences. In the study of the auditory agnostic patient, it was not observed in the responses to acoustically presented sentences but was observed in responses to visually presented sentences. These facts suggest the usefulness of the CNV as a test for sentence discrimination.

Thatcher and April (1976), using a delayed semantic-matching procedure involving synonym, antonym and semantically neutral English word pairs, demonstrated hemispheric asymmetries (left greater than right) in evoked potentials to the second word at latencies of 300 to 500 msec. In their opinion these major, long latency phenomena indicate that the asymmetries represent processes occurring at the level of memory or semantic representations.

In our experiments of word recognition, using Thatcher's paradigm, evoked response components N1, P300 and P650 to the second word were observed. P650 amplitudes to the second Kanji showed right greater than left asymmetries, but those to the second Kana words showed left greater than right asymmetries. Evoked responses to the first word were similar to those to the second word, but not marked. P650 was not observed in evoked responses to RDDs just before and after the second words of either Kanji or Kana. This suggests that P650 is attributed to semantic match-mismatch task-related brain activities. It is interesting to compare the P650 to the first word, to the second word and to the RDD in the semantic match-mismatch experiments with the P650 observed in the sentence experiments. P650 was observed in evoked responses to the first (subject) and the third (verb stem) characters but not observed in evoked responses to the second (ga-particle) and the fourth (verb ending) characters in the experiments of syntactic match and mismatch between subject and verb.

In the Japanese orthography two types of nonalphabetic symbols, Kana (phonetic symbols for syllables) and Kanji (essentially non-phonetic, logographic symbols representing lexical morphemes) are used in combination. In studies of Japanese aphasic patients, it has been reported that various types of dissociation between the ability for Kana and Kanji processing may occur (Sasanuma, 1971, 1975). From the results of studies on Japanese aphasics and tachistoscopic recognition experiments of Kanji and Kana in left and right visual fields in healthy subjects (Sasanuma et al., 1977; Hatta, 1977), the following hypothesis has been deduced: Kanji is mainly processed in the left hemisphere. The discrepant results between asymmetry of P650 amplitudes to the second Kanji and that to the second Kana-word are compatible with the above mentioned hypothesis.

It is very interesting to compare our work with Brown and Lehmann's (1977) which suggests that noun and verb in English are processed in different hemispheres from the observations of noun- and verb-auditory evoked EEG scalp potential fields.

In the examination of aphasics frequent confused responses for recognition of Kanji and Kana-words, smaller amplitudes of P650, and longer peak latencies of P300 and P650 were observed. It is assumed that information processing of words is more effective and takes a longer time in aphasic patients than in healthy subjects.

SUMMARY

To find out if ERPs can be useful for testing recognition of sentence and word, LPCs and CNV were investigated as follows: For sentence recognition subjects were required to respond with different key presses when sequentially presented sentences, visual or aural, were recognized as meaningful or meaningless by key information in the presentation. In healthy subjects P300 amplitudes (C3, C4) to the beginning of information and to the key information were larger than those to the other parts of the presented information. The difference between CNVs produced by meaningful and meaningless sentences was observed after the key information. In aphasia the recognition response in CNV after the key information was not observed. In auditory agnosia it was observed in responses to visual sentences but not in those to auditory sentences. For word recognition, subjects were required to press a different switch according to semantic match or mismatch between either two successive Kanji or two successive Kana words, presented in Thatcher's (1976) paradigm. In healthy, right-handed subjects P300 and P650 amplitudes (temporal and parietal leads) to the second Kanji showed a right greater than left asymmetry. P300 amplitudes to the second Kana words showed the same, but P650 amplitudes to the second Kana words showed a left greater than right asymmetry. These findings

of P650 are compatible with the hypothesis that Kanji (logographic symbols) and Kana (phonetic symbols) are processed differentially in the hemispheres. In aphasics, P650 showed less marked amplitudes and longer peak latencies. These results of two experiments suggest that CNV and LPCs can be useful for testing sentence and word recognition.

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THE MACULAR AND PARAMACULAR SUBCOMPONENTS OF THE PATTERN EVOKED
RESPONSE

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The studies to be presented have been carried out on healthy subjects, recording the pattern evoked response to a black and white reversing checkerboard stimulus, back-projected onto a circular translucent screen viewed monocularly by the subject at a distance of 1 meter. The full-field stimulus extends out from a central fixation point to an eccentricity of 16 degrees, and the individual checks subtend 50'. The pattern is reversed every 600 msec by moving it rapidly sideways through one square (10 msec transition time), and the response to 200 such reversals has been averaged in each run. For half-field stimulation, one side of the screen is masked off, and smaller areas of the remaining half-field stimulus could be masked off in the same way to test central or peripheral stimulation. The position of the central fixation light remains the same throughout.

The pattern evoked potentials are recorded from a transverse row of five occipital electrodes, the central one placed 5 cm above theinion in the midline and the lateral ones 5 and 10 cm out on each side. All are referred to a common midfrontal reference. Other electrodes have also been used, but the present account will be limited to these five channels.

The response to the full 0 to 16 degree field has a characteristic distribution over the occiput with a maximum amplitude in the midline falling off at the electrodes to either side. Its most prominent feature is the major positive component, designated P100 which is usually preceded and followed by smaller negative peaks, giving the whole response a triphasic negative/positive/negative (NPN) character (Fig. 1). We have shown in previous studies (Barrett, et al., 1976; Blumhardt, et al., 1977) that the

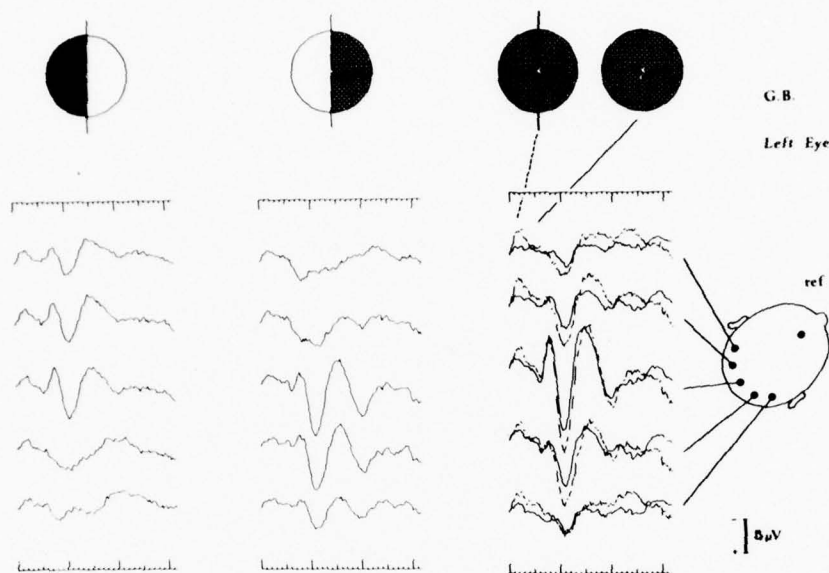


Fig. 1. Pattern evoked responses to left and right half-field and whole field reversing checkerboard stimuli presented to the left eye of a healthy subject. The subject fixates a small spot of light situated in the center of the screen, and the stimuli, which are made up of 50' black and white squares, extend out to an eccentricity of 16 degrees. Time scale in 10, 50 and 100 msec marks. In the right-hand record the full-field response is compared with the sum of the two half-field responses (dotted line). (From Blumhardt et al., 1977.)

whole-field response is made up of two highly asymmetric half-field responses. In each of these, the major positivity with its accompanying negative peaks is seen at the midline and ipsilateral electrodes, while the contralateral channels show a relatively flat record (Fig. 1). The full-field response approximates closely to an algebraic summation of the half-field responses recorded in the same subject, and the midline maximum is due to the addition of the ipsilateral components from both half-fields at this particular electrode (Blumhardt et al., 1977; Blumhardt and Halliday, in press). Although there are quite marked individual variations in the detail of the waveform, the same asymmetric features are seen in all healthy subjects, irrespective of which eye is being stimulated.

There is good evidence that the response recorded from the electrodes ipsilateral to the half-field stimulated is coming from

the contralateral hemisphere, since hemispherectomized patients show exactly the same asymmetric distribution for the response from their preserved half-field (Blumhardt and Halliday, in press). The reason for this curious lateralization of the major positivity appears to be the position and orientation of the cortical projection areas generating the response on the medial and postero-medial surface of the contralateral occipital lobe (Barrett et al., 1976). However, as we have previously demonstrated (Michael et al., 1971), the position of the reference in relation to the occipital electrodes is a critical factor in determining what one records.

In many healthy subjects, a smaller additional triphasic complex of similar latency but reversed polarity (PNP) can be recorded in the half-field response at the contralateral electrodes. This PNP complex shows much more variability in amplitude and waveform and is often inconspicuous or absent. When present, it is largest at the contralateral electrode 10 cm out from the midline. It can

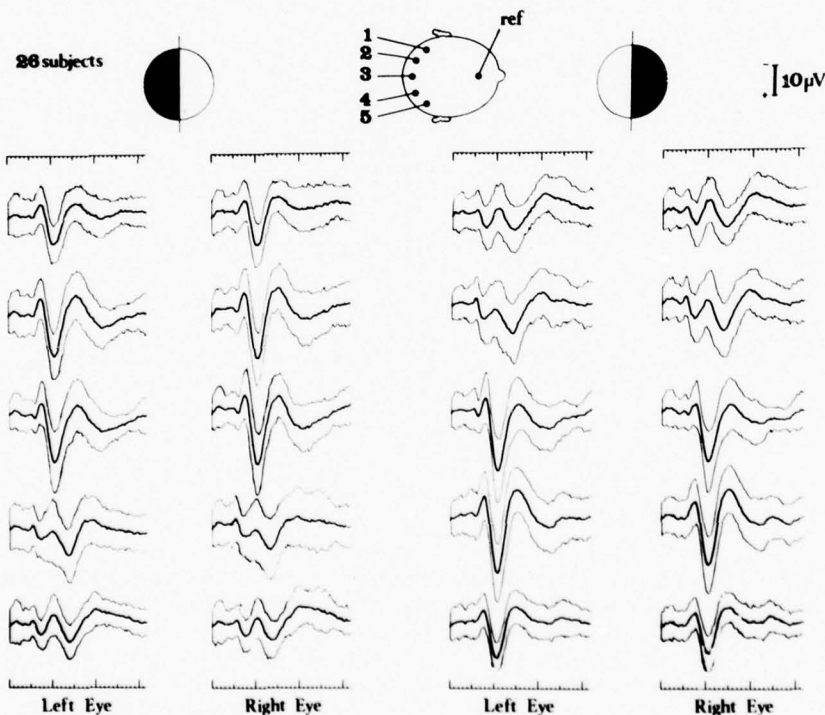


Fig. 2. Mean waveform and standard deviation for the half-field responses of twenty-six healthy individuals. The responses to stimulation of each half-field are shown separately for each eye. (From Blumhardt et al., 1978.)

be clearly seen in the mean half-field responses from a large group of healthy subjects (Fig. 2). The response recorded from the electrode 5 cm out on the contralateral side appears to be "transitional" between the large ipsilateral NPN complex and the smaller, more variable contralateral PNP complex, and it consequently has a larger variance.

At first sight the contralateral PNP complex of the half-field response looks as if it might be just a phase reversal of the ipsilateral NPN complex recorded from the other end of the genera-

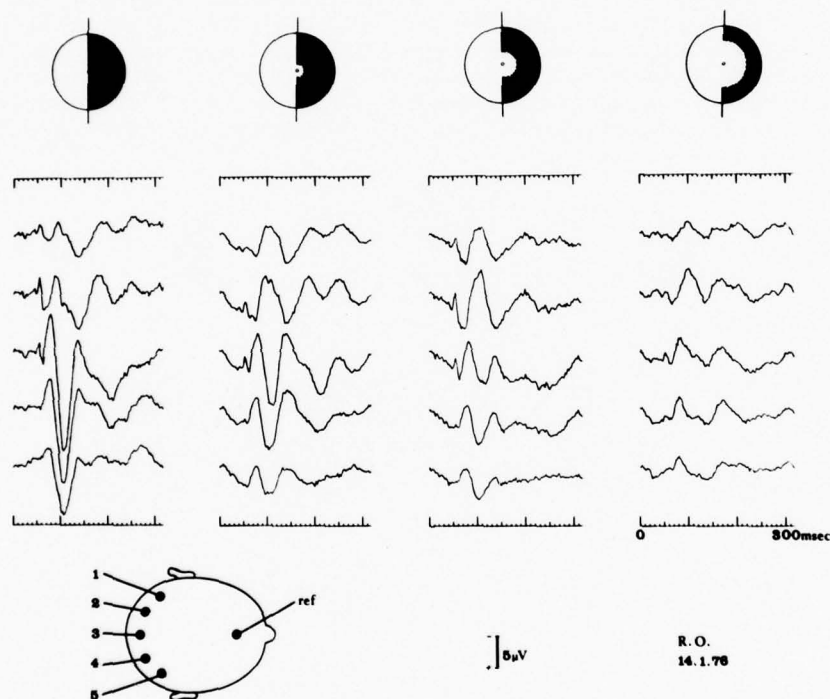


Fig. 3. The effect of removing a progressively increasing proportion of the central stimulus on the right half-field response of a healthy subject. The left-hand record shows the response evoked by the full 0 to 16 degree right half-field checkerboard stimulus. In the other three records the stimulus has been masked off in the central 2.5 degrees, 5 degrees and 10 degrees, respectively. Note that the ipsilateral NPN complex is rapidly attenuated when the central stimulus is removed, whereas the contralateral PNP complex is actually enhanced for the 2.5 degree and 5 degree "scotoma". (From Blumhardt et al., 1978.)

tor. The mean latencies of the subcomponents for a large group of healthy subjects are, in fact, roughly similar, particularly for the first two components. In a group of twenty healthy individuals Blumhardt et al. (1978) found that the initial ipsilateral negativity (N75) and the corresponding contralateral positive wave (P75) both had a mean latency of between 76.5 to 78.1 msec. Corresponding means for the major ipsilateral positivity (P100) and the contralateral negative wave (N105) similarly fell within the range 103.7 to 106.3. There was, however, a greater discrepancy for the third subcomponent of the two complexes, the ipsilateral negativity (N145) having a mean peak latency within the range 143.6 to 145.4, while the contralateral positivity (P135) had a mean latency of 134.6 to 137.5. Each range consists of four mean values, one for each half-field of each eye. These mean latencies conceal a much higher degree of variability in the individual responses, and an examination of individual records shows that the ipsilateral and contralateral components can vary independently in latency. The peak latency of the contralateral negativity (N105) may occur a few milliseconds before or after the corresponding ipsilateral positive wave (P100) in the same individual (see Blumhardt et al., 1978), Fig. 4).

Further evidence of the independence of the ipsilateral NPN and the contralateral PNP complexes is provided by a study of the effect of stimulating separately the central and more peripheral areas of the 0 to 16 degree half-field. This demonstrates not only that the ipsilateral and contralateral components depend to some extent upon stimulation of different areas of the half-field but also that the contralateral components can be "masked" by the ipsilateral ones (Blumhardt et al., 1978). The response to the full 0 to 16 degree right half-field shown in the left-hand record of Fig. 3 has a large ipsilateral NPN complex and a rather small and insignificant contralateral PNP complex. When the stimulating checkerboard is removed from the central 2.5 degrees of the right half-field, however, the ipsilateral positive components are much reduced in size, and a much larger contralateral PNP complex appears (see second record in Fig. 3). When the central 5 degrees is masked, leaving the checkerboard stimulus in only the peripheral portion of the right half-field from 5 to 16 degrees, the ipsilateral NPN complex is even more attenuated while the contralateral PNP component has shown a slight further increase in amplitude (third record, Fig. 3). Only when the checkerboard stimulus is masked out to 10 degrees is there a significant reduction in the size of the contralateral PNP response. It appears, therefore, as if the ipsilateral NPN complex is evoked particularly by stimulation of the macular parts of the field, while the contralateral PNP complex, which appears to be hidden in the full-field response in many individuals, only becomes apparent when the central stimulus is occluded.

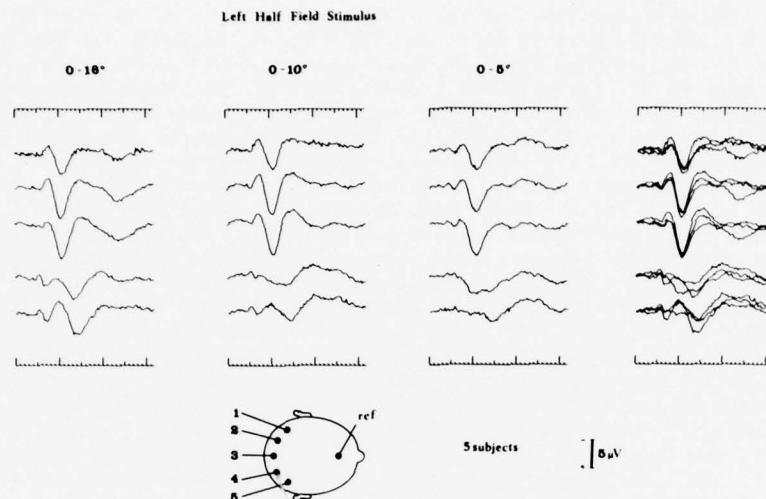


Fig. 4. The effect of reducing the peripheral area of the left half-field stimulus on the mean response waveform for five healthy individuals. The ipsilateral NPN complex is little affected by the elimination of the peripheral checkerboard stimulus beyond 10 or 5 degrees (see superimposed responses in the right-hand column). The contralateral PNP complex is, however, markedly attenuated. (From Blumhardt et al., 1978.)

The dependence of the contralateral PNP complex on stimulation of the paramacular areas of the half-field is well seen if the converse experiment is done, progressively occluding the peripheral extent of the half-field stimulus (Fig. 4). Since some individuals show little or no contralateral complex in their normal half-field response, this effect is best seen in the group mean response. Reducing the half-field stimulus from 16 degrees to 10 and 5 degrees has little effect on the ipsilateral NPN complex, since this depends predominantly on stimulation of the macular area. The contralateral complex is, on the other hand, markedly attenuated when the peripheral areas are occluded (Fig. 4).

These results in healthy individuals help to explain the characteristic changes in the pattern response which are encountered in patients with central scotomata (Halliday et al., 1976). In such patients, the normal major positive component of the pattern reversal response is often completely replaced by a negative component at approximately the same latency. Significantly, this nega-

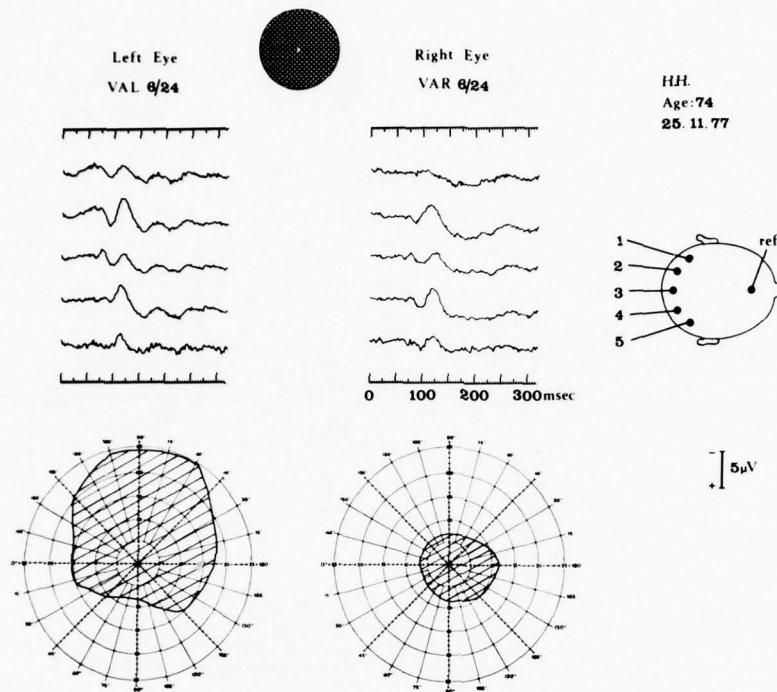


Fig. 5. Response evoked by the full 0 to 16 degree checkerboard stimulus from each eye of a 74 year old man with dense binocular central scotomata due to toxic amblyopia. Note the replacement of the normal NPN complex, which has a midline maximum, by the PNP complex at about the same latency which is of largest amplitude at the electrodes on either side of the midline.

tivity no longer has a midline maximum but is larger at the lateral electrodes, usually at the electrode 5 cm out on each side. It is, in fact, made up of a combination of the contralateral PNP complexes from the two half-fields (Fig. 5). This can be clearly demonstrated by half-field stimulation (Fig. 6). The PNP complex of the full-field response is then seen to have a contralateral distribution for each half-field, while the ipsilateral channels, where the major positivity normally appears as part of the NPN complex, are relatively flat. Lateralization of the responses by half-field stimulation is, therefore, an important method of analyzing the components of the pattern evoked potential.

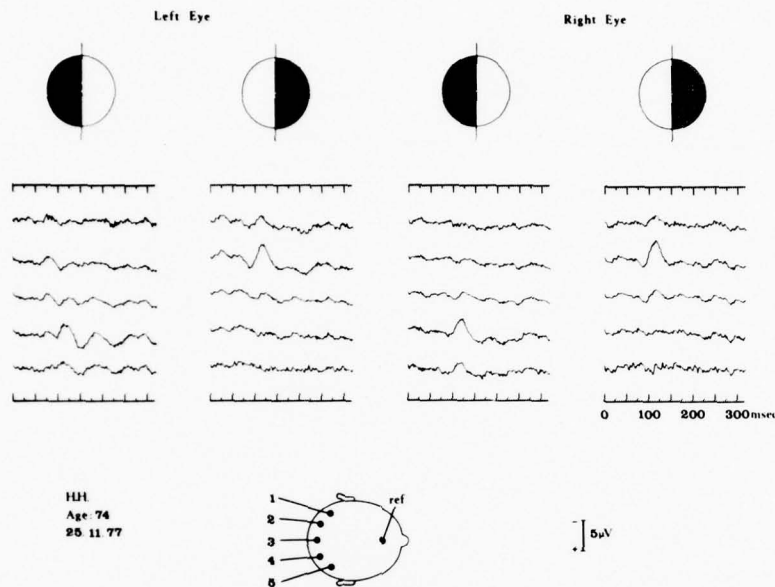


Fig. 6. Half field responses from the patient whose full-field response was shown in Fig. 5. Note that the PNP complexes of the full-field response are shown to have a contralateral distribution for each half-field stimulus.

However, a word of caution is necessary. If correct lateralization is to be achieved, it is essential to adopt a suitable electrode montage. The half-field response is so widespread over the back of the head that the choice of any reference within this area, such as the ipsilateral ear or mastoid, is liable to distort the record. If the reference is to be truly indifferent, a location must be chosen which is well outside the area of the scalp from which the response comes. Fig. 7 shows the same right half-field response recorded in a healthy individual with three different reference electrodes placed respectively on the left ear, mid-frontally and on the right ear. In this instance the standard transverse chain of five occipital electrodes spaced 5 cm apart has been augmented by two extra electrodes 2.5 cm out from the midline. With the reference on the right ear, the amplitude of the ipsilateral NPN complex is greatly attenuated, because this is also picked up by the reference electrode. Conversely, when the left ear reference is used, the contralateral PNP complex is slightly attenuated, because this, in turn, is picked up at the left ear.

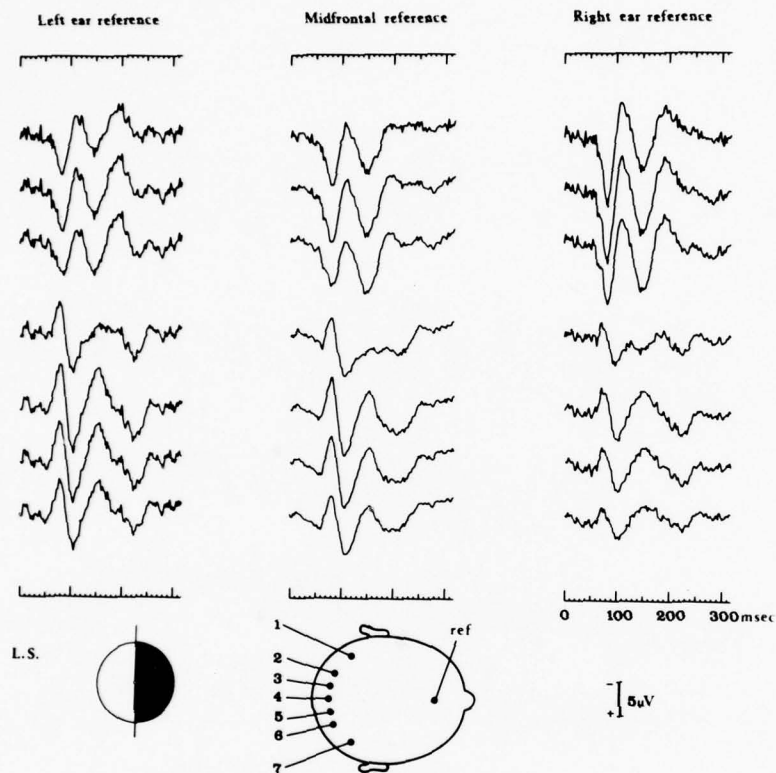
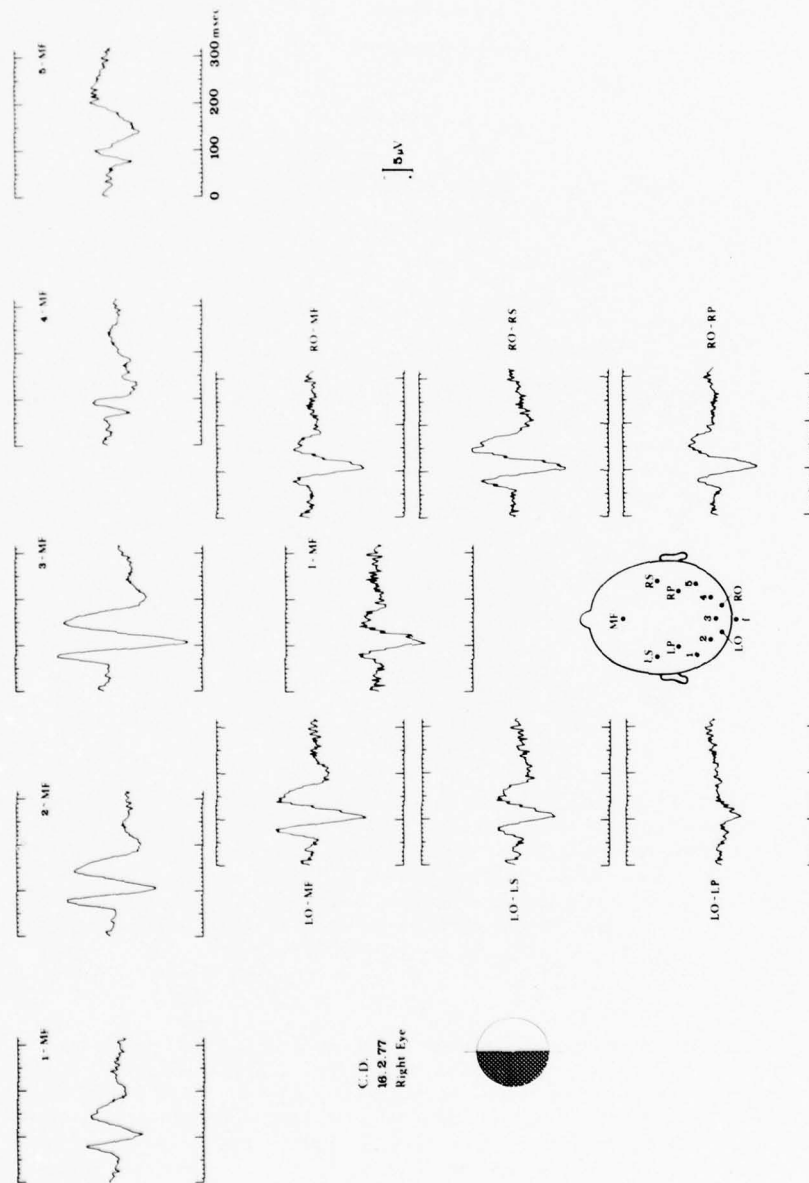


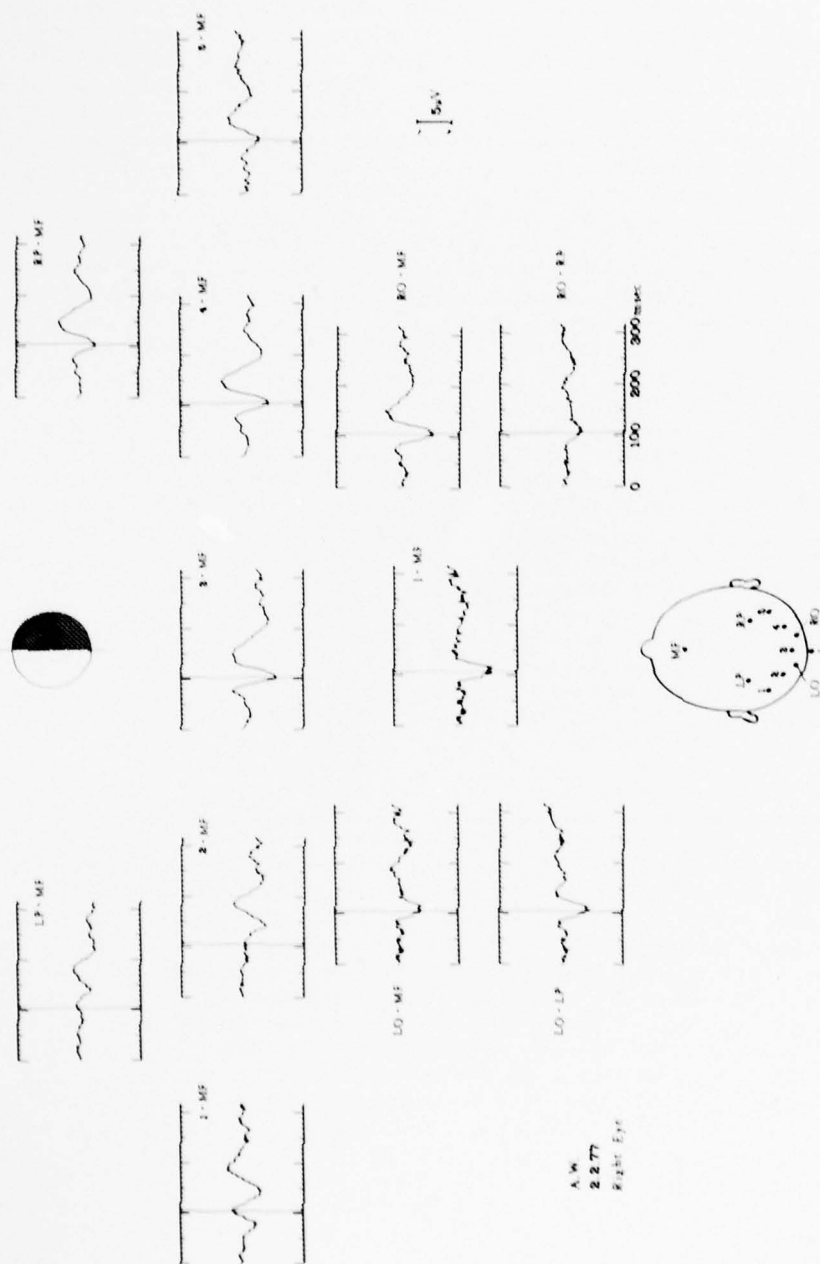
Fig. 7. Right half-field response recorded from a healthy subject with three different references. Two extra electrodes, 2.5 cm out from the midline, have been used to augment the standard transverse row of five electrodes spaced 5 cm apart. Note that the use of a right ear reference greatly attenuates the ipsilateral NPN complex, while the contralateral PNP complex is larger when this reference is used.

One can actually reverse the apparent lateralization of the half-field response by the injudicious use of a lateralized reference and a less than optimum electrode montage. Fig. 8 shows the left half-field response recorded in a healthy subject in a variety of ways. The upper row of five records illustrates the response recorded with the standard montage used in this study, the transverse row of five occipital electrodes, spaced at 5 cm intervals,



being all referred to a midfrontal reference. With this montage the major positive NPN complex is clearly lateralized ipsilaterally to the half-field stimulated, although the maximum amplitude is obtained at the midline electrode. The two contralateral channels record a typical PNP complex within the same latency range. When left and right occipital electrodes much nearer the midline are used (as in the locations about 2 cms up and out, favored in the modified Maudsley montage, and the slightly higher and more lateral locations of the 10-20 system), the lateralization of the major positivity of the NPN complex is much less clearly seen, because there is some spread of the positivity over the midline, the transitional zone between ipsilateral and contralateral complexes being well to the contralateral side of the midline. This is evident in the second row of records where the Maudsley left occipital (LO) and right occipital (RO) electrodes are referred to the midfrontal reference; the positivity is still larger for the ipsilateral channel, but the amplitude difference is not very great. When a choice of electrodes too near the midline is compounded by the use of a reference electrode on the same side of the head and within the wide area from which the occipital response can be picked up, a false impression of the lateralization of the response may be obtained (cf. Holder, 1977, 1978). In the third line of records the left and right occipital electrode of the Maudsley montage have been referred to Sylvian reference electrodes on the same side of the head, and in the fourth line of records the same occipital electrodes have been referred to left and right parietal references. In both cases the lateralization of the major positivity is apparently reversed and appears to be recorded from the side of

Fig. 8. Pattern response from the left half-field of a healthy subject recorded with different electrode montages. The upper five records are for the standard montage used throughout this study, a transverse row of five occipital electrodes, spaced at 5 cm, referred to a common midfrontal reference. Note the distribution of the NPN complex in the midline and ipsilateral channels and the smaller PNP complex seen at the two contralateral electrodes. The lower records are taken with the left occipital (LO) and right occipital (RO) electrode of the modified Maudsley montage referred (from above down) to a common midfrontal reference to a Sylvian electrode on the same side of the head and to a parietal electrode on the same side of the head. Note that the NPN complex is seen for both channels with the midfrontal reference because the electrodes are only 2 cm from the midline. With the ipsilateral Sylvian or parietal reference the NPN complex is mislateralized, appearing larger in the contralateral channel. This is because the response is picked up and partially cancelled by the Sylvian and parietal references on the left side of the head, but not on the right.



the head contralateral to the half-field stimulated. This is because both parietal and Sylvian references on the left side of the head are picking up something of the ipsilateral response. The response is, therefore, attenuated in the left occipital channel, which uses this reference, but is unattenuated in the right occipital channel, because this is referred to the right-sided reference. The parietal electrode picks up more of the response than the Sylvian, owing to its more posterior location, and there is a correspondingly more marked attenuation of the NPN complex at the ipsilateral occipital electrode.

Fig. 9 shows a similar example for right half-field stimulation in another healthy subject. Again the choice of occipital electrodes too near the midline, referred to a parietal electrode on the same side, leads to an apparent mislateralization of the response. It can be demonstrated by recording the parietal "references" against the midfrontal electrode that this effect is due to the ipsilateral parietal electrode picking up the response (see top right channel) and, thus, attenuating it when it is used as a reference for the occipital electrode. The left parietal electrode produces no such attenuation when used as a reference for the left occipital channel, because it is on the side of the head contralateral to the half-field stimulated. The net result again is that the major positivity appears to be larger at the occipital electrode contralateral to the half-field stimulated. This, however, is misleading, being entirely due to the cancellation occurring between pairs of ipsilateral electrodes because of the widespread distribution and large amplitude of the response over the ipsilateral half of the back of the head.

The use of half-field stimulation enables the subcomponents of the response to be identified as being either ipsilateral or contralateral. This can help to resolve many of the ambiguities which arise in interpreting abnormal pattern response records in clinical practice. Fig. 10 shows a typical "crossed" asymmetry recorded in a 48 year-old man with a suprasellar mass and bitemporal hemianopia. The P100 component is seen for each eye on the side ipsilateral to the preserved nasal field, i.e., in the midline

Fig. 9. Pattern response from the right half-field of another healthy subject to illustrate the effect of electrode montage and reference. Note, as in Fig. 8, the apparent mislateralization of the major positivity for the parietal reference montage (lower pair of records). The upper pair of records, from the parietal references referred to the common midfrontal electrode, demonstrate that the response is picked up by the parietal reference electrode on the right side of the head.

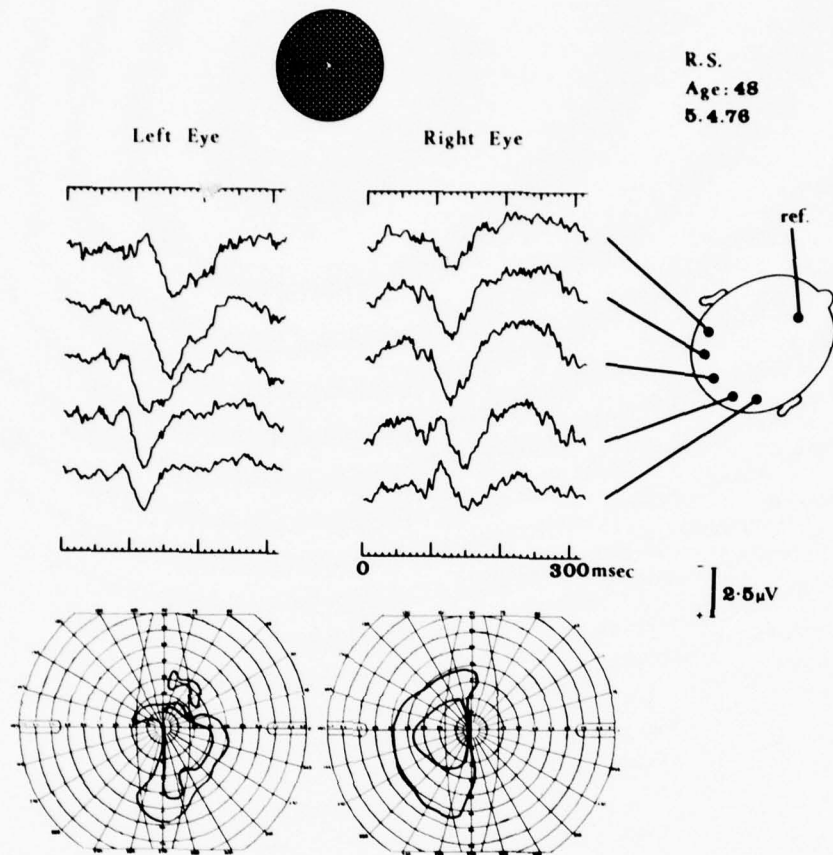


Fig. 10. Crossed asymmetry in a 48 year old man with a suprasellar mass and bitemporal hemianopia. The P100 component is seen ipsilateral to the preserved nasal field from each eye. Note the large later positivity recorded from the two channels on the other side of the head.

and right-sided channels for the left eye response and in the mid-line and left-sided channels for the right eye response. There is also a large, somewhat later positivity on the contralateral side, particularly prominent in the response from the left eye. Such large contralateral positivities have been previously observed and commented on in the records of patients with compressive lesions affecting the chiasma (Halliday et al., 1976). In the absence of information about the half-field responses, this contralateral

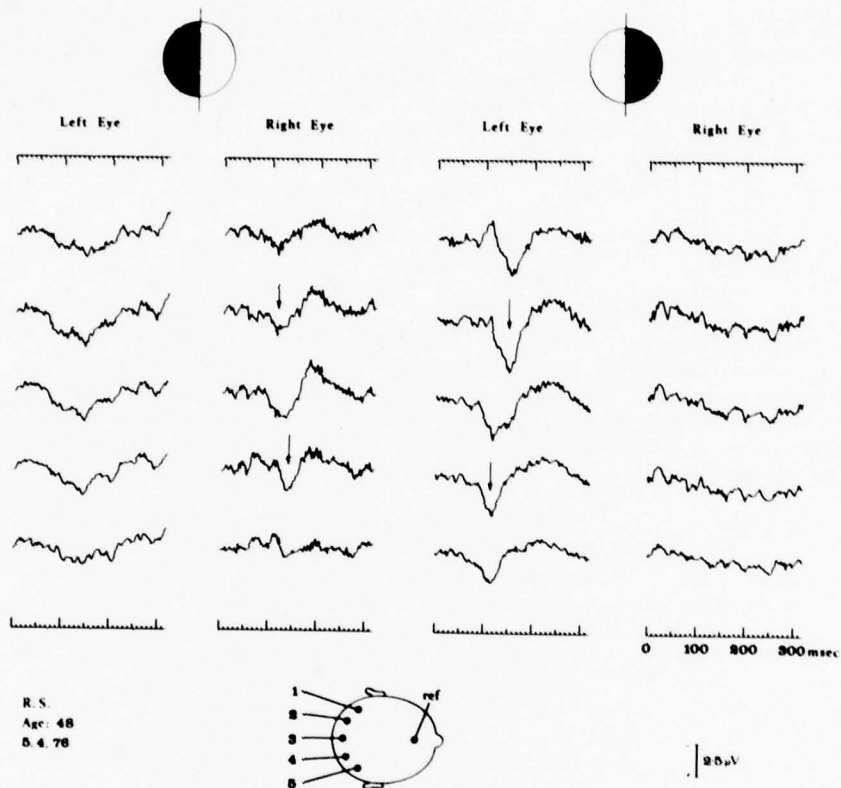


Fig. 11. Half-field responses from the same patient as in Fig. 10. Note that all the major features of the full-field response, shown in Fig. 10, are arising from stimulation of the nasal half-field of each eye. In particular, the later contralateral positive wave is seen to be the P135 component of the contralateral PNP complex of the half-field response, and not a delayed P100 component arising from the temporal half-field.

positivity can be interpreted as a delayed P100 from the temporal half-fields consequent upon the compression of the fibers crossing in the optic chiasma. Stimulation of the two half-fields separately (Fig. 11) shows conclusively that this is not the case. The "contralateral" positivity, like the ipsilateral P100, is seen in the responses from the preserved nasal half-fields, and not in the temporal half-fields. This component, therefore, represents a large third component of the contralateral PNP complex (P135). Since the

evidence from hemispherectomized patients establishes that both ipsilateral and contralateral components of the half-field response are produced in the same hemisphere, there is no question of invoking a delay in the chiasmatic fibers to explain this response. This is simply one example of the clarification which can be gained by the use of half-field stimulation. We are now using it routinely in clinical practice.

SUMMARY

The occipital potential evoked by a reversing black and white checkerboard is made up of the addition of the left and right half-field responses, each originating from the contralateral hemisphere. Since the whole field response closely approximates the algebraic sum of the two half-field responses, there is no evidence of any significant interaction between the generators in each hemisphere.

Within each half-field response, the three components of the triphasic NPN complex recorded from midline and ipsilateral electrodes (N175, P100, N145) appear to behave independently from the components of the PNP complex recorded contralaterally (P75, N105, P135). The "ipsilateral" P100 component is evoked particularly by pattern stimulation of the foveal area, while the "contralateral" N105 component depends on parafoveal stimulation. The components can be independently enhanced or attenuated by varying the area stimulated in each half-field. Occlusion of the central stimulus attenuates the P100 component, with a consequent enhancement of the N105. The same changes in the pattern response occur pathologically in patients with central scotoma. A converse attenuation of the contralateral negativity can occur when the stimulus is removed from the parafoveal region.

Many of the ambiguities arising in the clinical use of pattern EPs can be resolved if the nature of these components is understood. Correct lateralization of the half-field components depends on the use of a truly indifferent reference, such as a midfrontal electrode, while misleading appearances may result from reliance on more posteriorly or laterally placed references, such as an earlobe or parietal electrode. Clear identification of the components by lateralization also enables one to distinguish between the P100 and the P135 components, which may otherwise be confused and lead to ambiguity when the problem is one of differentiating delays from scotomatous changes.

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THE EFFECTS OF METHYLPHENIDATE DOSAGE ON THE VISUAL EVENT RELATED
POTENTIAL OF HYPERACTIVE CHILDREN

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Hyperkinetic children have a disorder of attention, and that disorder can be reduced by giving stimulant drugs (Barkley, 1977). Unfortunately, the process of attention itself remains something of a mystery. So, naturally both the disorder of attention in hyperkinesis and the beneficial effects of stimulants are also unclear. The sensory ERP reveals something of the sequence of brain operations that follow a stimulus and thus provides a temporal dissection of operations potentially involved in attention. We have been employing ERP to study the interaction of attention and stimulants in hyperkinetic children in the hope of clarifying the nature of attention, its disorder in hyperkinesis and the effect of the stimulant methylphenidate.

METHOD

Subjects

The subjects in this experiment were nineteen hyperactive boys referred to us by the Learning Disabilities Clinic, Kaiser Permanente Medical Center, Oakland, California. Diagnostic criteria were similar to those applied to a previous series of children (Halliday et al., 1976). In addition, however, each child in the experiment was rated by his teacher on the Conners Teacher Rating Scale (Conners, 1969) at least two standard deviations above current norms. This scale has been found to differentiate hyperactive children from normals (Cohen et al., 1974) and is sensitive to the effects of methylphenidate even at relatively low doses.

Parents of the children were referred to our project if the pediatrician felt that a clinical trial of methylphenidate was indicated. The project was then explained to the parents and voluntary consent obtained. Treatment was not contingent on participation in the project. Preliminary to actual acceptance, the pediatrician administered 5, 10 and 20 milligrams of methylphenidate to test for possible allergic or other deviant responses.

Evoked Potential Procedures

Visual evoked potential (VEP) activity, heart rate and reaction time during the attended portions of the experiment were recorded from each child on four different sessions. A placebo capsule was always administered on Session #1. In the remaining sessions the child took three different dosages of methylphenidate 45-60 minutes before the start of a run. The active dosages were 0.16 (low), 0.33 (medium) and 0.66 (high) milligrams methylphenidate/kilograms body weight (mg/kg). For an 80 pound youngster (36 kg), this dosage would be 5, 10 and 20 mg of Ritalin. Order of drug administration was randomly assigned to one of three possible sequences.

The entire experiment was controlled by a small laboratory computer (NOVA 1220). A schematic of this system is shown in Fig. 1. Visual evoked potentials were recorded from a single vertex electrode (Cz) referred to linked ears in the first eight children. In the next eleven children, parietal (Pz) and frontal (Fz) electrodes were added to this montage. Eye movement and cardiac activity were monitored by Beckman electrodes. The EEG was amplified by standard EEG electronics with filters set at 1 and 35 Hz. The trial sequence was initiated by the R-wave of the cardiac cycle which triggered a brief pulse to the computer. A 50 msec flash of light followed 150 msec after this initializing pulse. This delay prevented the R-wave from contaminating the VEP activity. The next trial was randomly initiated after the second, third or fourth R-waves. The interbeat intervals between R-waves on each trial were stored and the means and standard deviations printed out at the termination of the experimental condition, but this data will not be reported here.

The EEG was sampled every 4 msec beginning 50 msec prestimulus and continued over a 1000 msec interval. Individual trials and the averaged VEP were stored on the computer floppy disk system for subsequent analysis. Reaction time and response accuracy in the attending tasks were also stored.

The within-sessions conditions consisted of an active-attending task (ATT) and a passive-observing task (PAS). Whenever possible, one or both tasks were repeated. The number of replications was, however, unequal due to the fact that some children found it diffi-

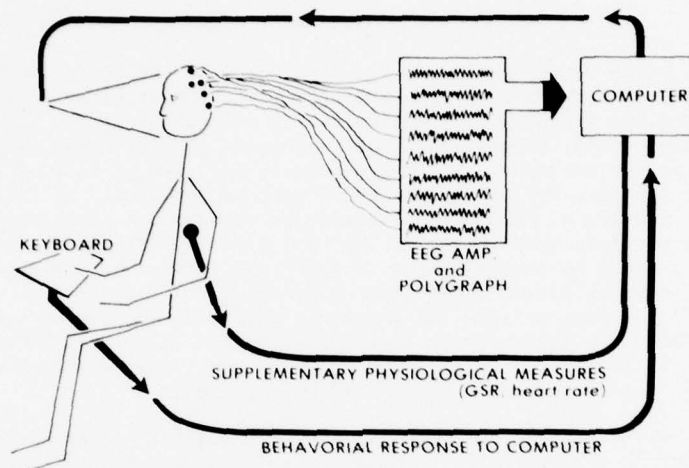


Fig. 1. Schematic of ERP system

cult to stay attentive during the later portions of the experiment. For the ATT task, the child was asked to press a microswitch whenever he detected a dim flash (signal) embedded in a series of brighter flashes (nonsignals). Signal events occurred in 10% of the trials, and each correct detection earned a 10¢ reward. Heart rate and VEP data for approximately 100 nonsignals were collected in each attending sequence. In the PAS task, the child was requested to simply observe the flashes. A special eye movement algorithm continuously computed activity from the eye electrodes and tagged records that exceeded present levels. These records were excluded from the computation of the averaged VEP. Intertrial interval varied between two and four seconds. Each attentional run took approximately ten minutes. Thus, each session, with appropriate rest periods, required 30-45 minutes to complete.

The child was seated in a comfortable chair in a sound attenuated, electrically shielded room. Signal and nonsignal stimuli were delivered by a small box located 153 cm from the child. Before the start of each session the child was given sufficient practice to ensure that he understood the procedures. He was encouraged to sit quietly during the run and cautioned against irregular breathing or looking around the room.

RESULTS

Prior to any analysis, the data for each child was examined trial by trial, and any records with obvious contaminants were tagged and excluded from analysis. In general, very few artifacts were observed, suggesting that our on-line artifact rejection procedure was adequate. The ERP data were analyzed in several ways. Only the data for the Cz electrode will be reported. We followed the traditional procedure of having an experienced psychophysiological pick the large negative (N1) and positive (P2) peaks visually while blind to dose and type of attention. The computer then recorded amplitude from prestimulus baseline and latency from stimulus. Then, for each measure, an ANOVA was done with AGE (under ten years and over ten years), DOSE (none, low, medium, high) and ATTENTION (active or passive) as conditions. To reduce the amount of missing data, the data were averaged over replications.

The amplitude of N1 (N159) showed a significant AGE X DOSE X ATTENTION effect ($F = 3.2$; $df = 3,51$) and a near significant ($P < .07$) AGE X DOSE effect. These effects are shown in Figs. 2 and 3. In the younger children, increasing doses of methylphenidate increased the N1 although this effect was more dramatic in the passive-observing condition. In the older children, the effects of dosage were quite different for the two tasks. N1 in the attending condition showed a significant increase up to the medium (.33 mg/kg) dose. Further increases in dosage precipitated a dramatic decrease in amplitude. In the passive task, N1 amplitude declined gradually throughout the dosage range.

Latency of N159 showed a significant linear AGE X DOSE component ($F = 7.57$; $df = 1,17$). This effect is shown in Fig. 4. Younger children showed an increase in latency up to the medium dose while older children showed a decrease.

The P228 amplitude showed a significant DOSE X ATTENTION interaction ($F = 3.0$; $df = 3,51$) and is shown in Fig. 5. Amplitude dropped with increasing dosage with the major effects occurring in the attending condition. P228 latency showed no significant effects.

The ERP data from the first eight subjects had been previously studied by factor analytic technique, and this was repeated on this larger group. Each subject supplied up to sixteen ERPs (four doses, two replications, two attention conditions). The set of ERPs from each subject was normalized to remove individual characteristics. To do this, a mean ERP was computed over all of the subject's ERPs, as well as the standard deviations. Thus, there was a mean and a standard deviation at each time point. Then for each individual ERP at each time point, that appropriate mean was subtracted, and the results were divided by the appropriate standard deviation.

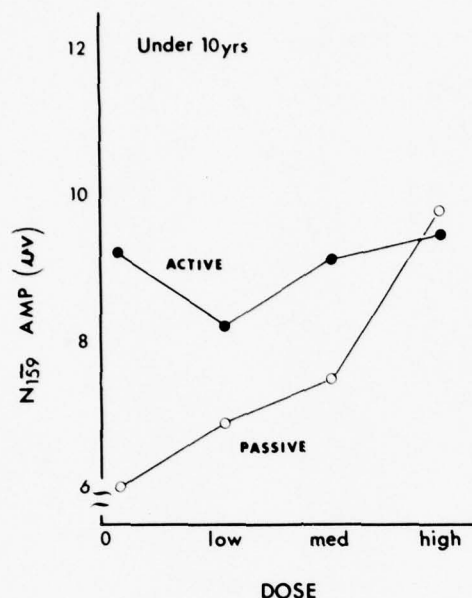


Fig. 2. Methylphenidate dose/response curves for N159 amplitude in hyperactive children under ten years.

The result was an ERP measured in standard scores rather than in voltage. The correlation matrix of these normalized ERPs was then factored by principal components analysis. Nine factors were extracted to account for 81% of the variance, and these were treated by Varimax rotation. Factor scores were then derived to characterize each component of the experimental paradigm, and these scores were submitted to ANOVA. Of the nine factors, six yielded F ratios in their respective ANOVAs at the .05 level or better. These factors are illustrated in Fig. 6.

Before discussing these factors, one thing should be noted. Factor #9, which is not shown, seems to represent the N159 msec component which in our previous factor analysis performed much as the N1 peak amplitude performed in this analysis. While in the present factor analysis this particular factor showed an effect of attention which was significant at the .06 level, it showed no significant interaction with dose or age.

Returning to the figure, Factor #1 behaves much as the P2 component in the conventional analysis. There is a significant DRUG X

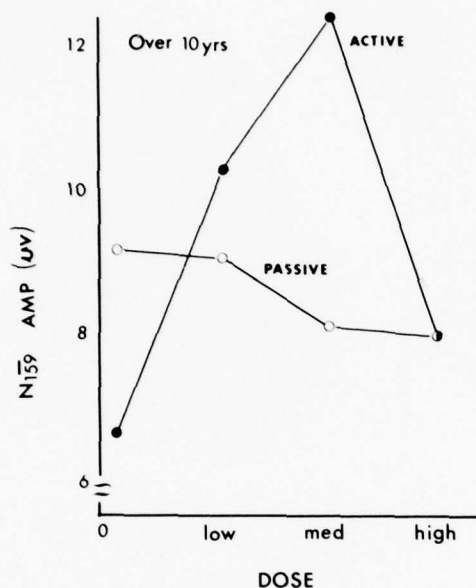


Fig. 3. Methylphenidate dose/response curves for $\overline{N159}$ amplitude in hyperactive children over ten years.

ATTENTION effect ($F = 2.9$; $df = 3,51$) that decreases linearly with dose. This effect is best seen in the older subjects in the attending condition. Factor #4 (approximately 400 msec) is principally an age effect which is consistent with the increase in amplitude of later components in older children that has been noted by many other observers. Factor #5 (approximately 50 msec) is something of a surprise. This very early component shows a strong DOSE effect ($F = 3.8$; $df = 3,51$) and an AGE X DOSE X ATTENTION effect ($F = 3.6$; $df = 3,51$). This is a complex factor and will require replication before too much is made of it. Factor #6 (approximately 300 msec) is a pure ATTENTION effect ($F = 4.9$; $df = 1,17$). It appears to be the usual P300. Factor #7 (approximately 750 msec) is a very late component which shows a significant quadratic DOSE effect ($F = 7.1$; $df = 1,17$) and an AGE X DOSE effect ($F = 2.8$; $df = 3,17$). These effects are highly significant and unexpected. They are illustrated in Fig. 7. Finally, Factor #8 yields both a linear DOSE ($F = 7.5$; $df = 1,17$) and an AGE X DOSE X ATTENTION ($F = 3.2$; $df = 3,51$) effect. This 450 msec component appears principally as a linear dose increase that is most marked in the younger subjects during the active attention task.

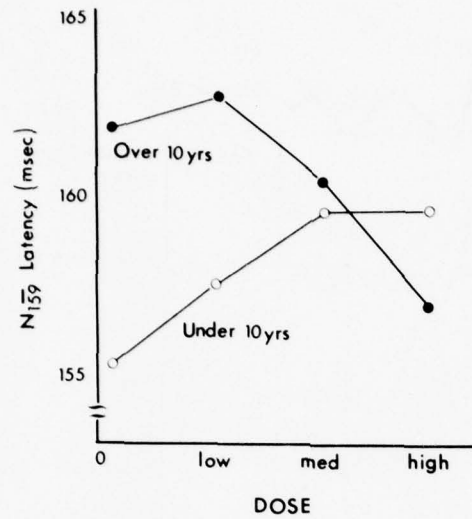


Fig. 4. Methylphenidate dose effects on N159 latency in two age groups of hyperactive children.

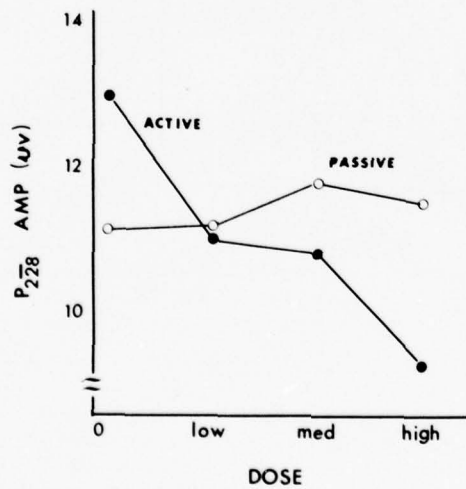


Fig. 5. Methylphenidate dose/response curves for P228 amplitude in active and passive observing conditions.

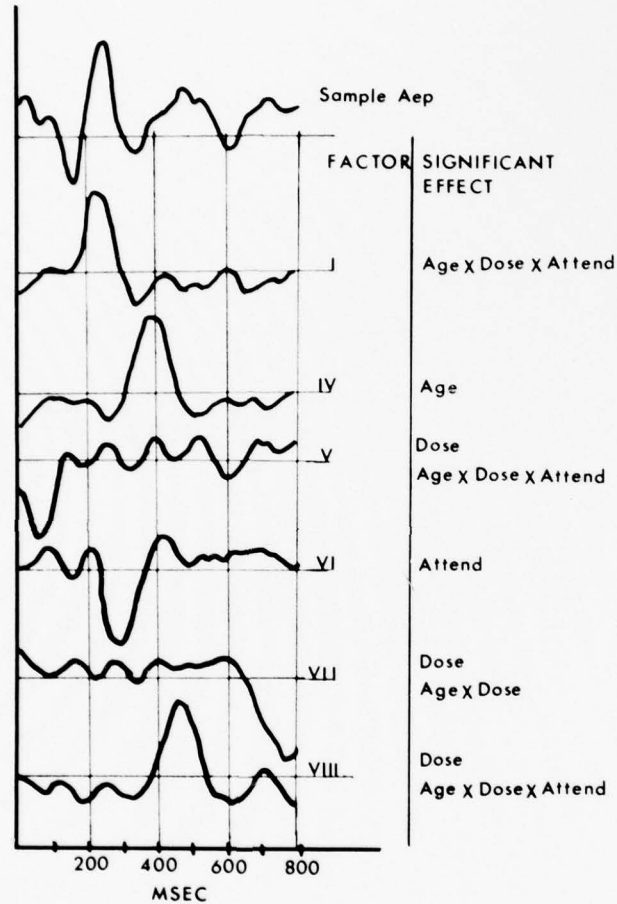


Fig. 6. Normalized ERP component loading functions and experimental conditions which yielded significant effects.

Reaction Time

Reaction times to the dim flash were influenced both by age and by dose. They were also, as might be expected, significantly increased by replication, and reaction time tended to be faster in later trials than in earlier trials. In general, older children were faster ($F = 6.5$; $df = 1,17$) as would be expected. DOSE effects were significant ($F = 13.3$; $df = 3,51$) with significant linear and quadratic components. This is illustrated in Fig. 8.

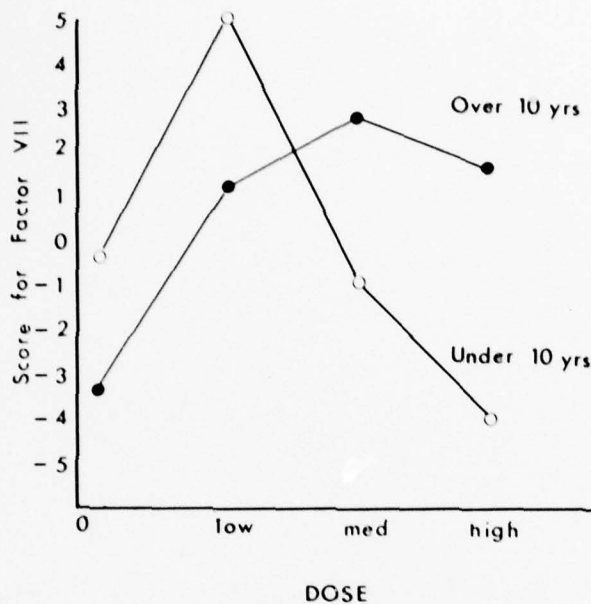


Fig. 7. Methylphenidate dose/response curves for factor loadings on Factor #7 (450 msec) in two age groups of hyperactive children.

Higher dose produced a slight increment in speed for the older children and a near significant slowing for the younger children. Reaction time variability also decreased with DOSE ($F = 3.8$; $df = 3,51$) but showed neither AGE, nor AGE X DOSE effects.

DISCUSSION

In general, our findings suggest that the effects of methylphenidate to nonsignal stimuli are far more complicated than previously realized. In the analysis of conventional N1 and P2 components of the ERP neither age, dose nor attention produce first order effects. Dose plays a role in all of the interactions, but dose effects are different, depending upon the particular component being analyzed and the method used to measure it.

The nonmonotonic increase in N159 amplitude during active-attending with increasing dosage has been previously reported (Elliott et al., in press). However, the inverted-U shape function appears to be restricted to older children. Younger children show a different function in which dosage exerts its principal effect during the passive-observing task. Latency also changed with dose and age. With

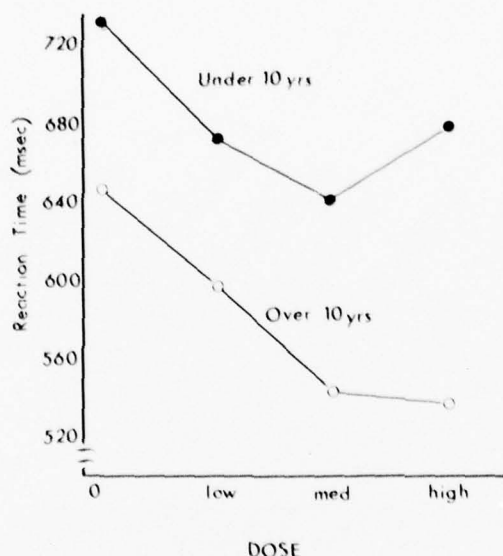


Fig. 8. Methylphenidate dosage effects on reaction time in two age groups of hyperactive children.

increasing dosage, the latency of younger children increased while older children showed a marked decrease. P2 (P228), however, did not show an age effect and the effect of dosage was to decrease the amplitude of this component in the attending condition. Thus, when N1 and P2 are measured independently, rather than peak-to-trough, the components are seen to respond differently to variations in the experimental paradigm.

In general, the principal components factor analysis produced components which appear reasonable. Most of the factor components were unimodal and occurred in the expected time bands. However, some of the factor analysis components did not show the same dose/response functions as did the analogous components picked visually. Factor #9, for example, appeared to be the N159 component. Yet, this factor did not show a significant AGE X DOSE X ATTENTION interaction. It may well be that the effects of methylphenidate are obscured by a method that ignores individual differences in N1 latencies.

We had previously suggested that methylphenidate acted principally on the 100-200 msec portion of the ERP (Callaway et al., 1978). The present results, however, indicate that the effects are not as restricted as we had proposed. Dose interacted with age and attention in both the early (50 msec) component and the 450 msec late

component. Additionally, a very late component (750 msec) was affected by age and dose. While the effects of methylphenidate on late ERP activity are consistent with the work of Klorman (1978), the effects on the 50 msec component are surprising. However, we note that a recent study by Sohmer and Student (1978) has reported delays in the central transmission time of far field potentials in hyperactive children, thus opening up the possibility that early cortical activity may be delayed and perhaps affected by stimulants.

The present findings reconcile some apparently discrepant reports in the literature. For example, with low doses of stimulants we find speeding of reaction time but very little effect on the event related potential. This confirms a report of Hink et al. (1978) who obtained similar results in adults given 10 mg of methylphenidate. By contrast, we find a reduction in P2 amplitude and a shortening of N1 latency at very high doses. This is confirmatory of the findings reported by Velasco et al. (1977) who gave 40-50 mg dextroamphetamine to adults and noticed a reduction in the P200 amplitude.

Age appears to be one of the most interesting factors. Indeed, had we not taken age into account, many of the effects noted would have simply disappeared. Satterfield and Braley (1977) have reported striking age differences in auditory ERPs of normals and hyperactives. They suggested that younger hyperactives may be hyperaroused relative to older hyperactives. This hypothesis predicts that increasing arousal with a stimulant would make the older hyperactive child look increasingly like younger hyperactives without stimulant. This suggestion finds some confirmation in our N159 data. In particular, older hyperactive children show a decrease in N159 amplitude for the passive-observing task with stimulant, making their values approach those of young subjects without drugs. Stimulants also make the older subjects have shorter N159 latencies, again more like the younger drug-free subjects. However, their theory does not explain why increasing dosage should increase the amplitude of the N159 component in younger children. The only other data published on age differences in hyperactive children was by Buchsbaum and Wender (1973). They found, as we did, that younger children show faster N159 latencies.

Several other age related phenomena can also be cited as playing a role in the differences observed in this report. For example, the diagnosis of hyperactivity is much easier to make at age ten years than at age seven years and there is some evidence that clinical response is somewhat better in older children (Loney et al., 1978; Halliday et al., in press). Thus, older hyperactives may be a more homogeneous group than younger hyperactives with respect to the primary underlying symptom of this disorder. Finally, developmental changes in cognitive skills may account for the age

effects noted. Hagen and Hale (1975), for example, have noted that young children are more likely to attend to stimuli that are peripheral to a central task than older children. If stimulants act on attentional capabilities, then age dependent responses to stimulants would be anticipated.

The present data suggests that N159 and P228 represent different levels of stimulus selection in the total attentive process. N159 may reflect a channel selection or wide band filter, and P228 a narrower band process. Arousal and attention interact to narrow the focus of both processes. Thus, with increasing stimulant, a non-target stimulus in the relevant modality is quickly excluded by the narrow process, while it continues to receive more energy from the broader focused process. As focusing continues the broader process also comes to exclude the non-target.

To be more graphic, consider the multidimensional field over which selective attention operates as reduced to two dimensions. The non-target stimulus is imagined as a light-sensitive device slightly removed from the target stimulus itself, which is the focal point of two spotlights. The two spotlights have a variable focus and illuminate in sequence the spot that represents the stimulus. The energy of the first light on the spot produces N1 - and that of the second, P2. As stimulant dose increases and the focus narrows, the N1 light is first concentrated on the spot, while the P2 light begins to exclude it. So N1 increases and P2 falls. Then, as focusing continues, the N1 light also begins to exclude the stimulus-spot, and N1 also begins to fall.

This scheme is testable. One can use stimuli that are more distant from the target as, for example, stimuli in a different modality. We would then expect the N1 for the more remote stimulus to show a nearly monotonic decrease like the P2 of the less distant stimulus. P3 of the central stimulus would, however, show a nearly monotonic increase.

This theory is sure to be wrong, at least in some details, but provides a useful framework for a start. Such ERP dissection of attention allows us to take a new look at concepts of arousal-induced narrowed attention. Such ideas have been of some interest in the past (Callaway and Stone, 1960; Easterbrook, 1959), but could not be pursued effectively in the laboratory at that time. This ERP dose/response paradigm promises to be a new and effective tool for application to this problem.

SUMMARY

Visual event related potentials were examined in nineteen

hyperactive (HA) children under four different dosages of methylphenidate and two levels of attention. Dosage had a significant effect on the VERP but specific findings were found to depend on the child's age, level of attention and the component measured. In HAs over ten years, N159 amplitude in the attending condition bore an inverted-U shape relationship to dosage. In HAs under ten years, the amplitude of this component increased linearly with dosage but this effect was only found in the passive-observing condition. N159 latency increased with dosage in younger children but decreased in older HAs. P228 amplitude decreased linearly with dosage in the attending condition but showed no significant age effects.

A principal components factor analysis was computed on normalized VERP waveforms. Factor scores describing each of the experimental conditions were obtained and analyzed by ANOVA. Nine factors were extracted and five of these were affected by dosage in combination with either age or attention. Dosage effects were found in both early and later components.

The relevance of these findings to other studies was discussed. A two stage model of attention was proposed, and the use of VERP dose/response curves as a method for untangling various attentional mechanisms was presented.

ACKNOWLEDGEMENTS

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EVOKED POTENTIAL INDICANTS OF SIZE- AND ORIENTATION-SPECIFIC
INFORMATION PROCESSING: FEATURE-SPECIFIC SENSORY CHANNELS
AND ATTENTION

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One advantage of evoked potentials (EPs) to transient stimuli is that they contain information as to the time-course of the electrophysiological response to such stimuli. This time course may be presumed to reflect the temporal sequence in which information contained in the stimulus is processed. The present paper is primarily directed toward a better understanding of the time course of information processing specific to the size (spatial frequency) and orientation of the elements of visual stimuli. Such processing will be considered both in relationship to sensory information channels and selective attention. The final section will be a brief review of preliminary data on the potential applications of these types of procedures to clinical problems.

EP MEASURES OF FEATURE-SPECIFIC SENSORY CHANNELS

Psychophysical data from man (Blakemore et al, 1973; Blake and Levinson, 1977) and electrophysiological data from animals (Wiesel and Hubel, 1966; Ikeda and Wright, 1972) indicate that there are sensory channels selectively responsive to specific spatial frequencies and orientations of pattern stimuli. The bandwidths of spatial frequency and orientation channels vary between 1-2 octaves and 3-40° respectively, depending on the procedure used.

Interocular suppression of transient VEPs has been used as an electrophysiological measure of spatial frequency (Harter et al., 1976) and orientation (Harter, 1977; Harter et al., in prep.) channels in man. In these studies high contrast patterns of different check sizes or orientations were continuously presented to one eye

while VEPs were obtained to a pattern flashed to the other eye. The amplitude of particular VEP components progressively decreased as the spatial frequency or orientation of the flashed and continuously presented pattern was made more similar. The bandwidths were about 2 octaves and 40° , respectively, for size- and orientation-specific suppression. These values correspond reasonably well to those based on psychophysical measures obtained under comparable conditions. Orientation-specific suppression had the greatest effect on components peaking between 75 and 110 msec poststimulus, whereas size (spatial frequency)-specific suppression had the greatest effect on components peaking between 125 and 160 msec poststimulus. This difference suggests that the orientation of the stimulus may be processed before its spatial frequency. On the other hand, however, it simply could reflect the effects of the different experimental conditions employed in the procedures of the two studies.

SELECTIVE ATTENTION AND SENSORY CHANNELS

There has been considerable discussion as to the nature of mechanisms which might mediate the effects of selective attention (see reviews by Tueting, in press; Hillyard, et al. in press; Donchin et al., in press). Harter and Previc (in press) hypothesized that the specificity of selective attention, as reflected by VEPs, may be determined by the specificity of sensory information channels. To test this hypothesis subjects were presented checkerboard light flashes which varied randomly in check size. One of the check sizes was made task relevant (attended) and all others task-irrelevant (ignored). When subjects selectively attended a given check size, the VEP to that check size contained a negative component which began at approximately 210 msec and peaked at about 160 msec poststimulus. An inverted U-shaped function was obtained between the amplitude of this negative component and the flashed check size with the peak of this function associated with the attended check size. The fact that this size-specific attention was reflected in the VEP as early as 160 msec poststimulus and has a bandwidth comparable to sensory size channels (about 2 octaves) supports the hypothesis that sensory channels are the functional units that mediate the specificity of attention to check size.

A comparison of the results of the above studies of interocular size and orientation suppression and of size-specific attention suggests the following conclusions: first, orientation-specific suppression is of greater magnitude and occurs earlier in time than size-specific suppression. This suggests that orientation channels may precede spatial frequency channels; secondly, the effects of interocular suppression occur earlier in time than the effects of selective attention. This suggests that the earliest sensory channels, as reflected by feature-specific interocular suppression,

may not be directly influenced by selective attention. These conclusions, however, must be considered tentative since they were based on a comparison between studies conducted under different experimental conditions.

In order to further substantiate these conclusions, two studies of spatial frequency and orientation effect on VEPs were conducted under virtually identical stimulus conditions: Experiment A investigated the effects of intra- and interocular suppression (Towle et al., in prep.), while Experiment B investigated the effects of selective attention (Harter and Previc, in prep.). In addition to the question of the time course of the suppression and attention effects, these experiments were concerned with the specificity of these effects. For example, if these effects are interdependent, then grating of a given spatial frequency and orientation would only influence the response to other gratings of that same spatial frequency and orientation. If, on the other hand, these effects were independent, a grating of a given spatial frequency and orientation would influence other gratings of that same orientation but of different spatial frequencies, and vice versa. Interdependence of effects would indicate "pattern-specific" type channels, whereas independence of effects would indicate "feature-specific" type channels.

Method

The stimuli were four black and white square-wave grating transparencies consisting of 9 or 36 min bars (3.3 or 0.83 c/d) oriented vertically or horizontally. These four patterns will be referred to as 9V, 9H, 36V and 36H, respectively. Monocular (right eye) evoked potentials were obtained only to the 9V and 36H gratings by back illuminating these transparencies once every 780 msec with a 10 msec light flash. The intensity of this flash was 2.5 log units above threshold. The visual fields viewed by the left and right eye subtended 7° and were binocularly fused by means of a haploscope (Fig. 1). The constant luminance of each field was 4 mL.

Monopolar EEGs were obtained with Grass gold-cup scalp electrodes, the active electrode placed 2.5 cm above the inion on the midline (Oz) and the reference electrode attached to the right earlobe (A2). They were amplified with a Model 7WC Grass Polygraph (1/2 amplitude high and low frequency filters set on 36 and 1 Hz, respectively). Evoked potentials to the 9V and 36H flashed gratings were averaged (N=64) for 512 msec poststimulation. Each experimental condition was replicated four times during the course of the experiment.

The purpose of Experiment A was to compare the time courses of

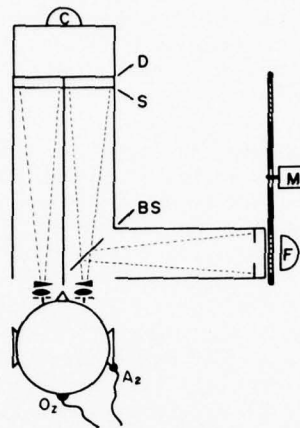


Fig. 1. Haploscope. Subjects continuously viewed dichoptically presented suppressing stimuli (S) illuminated by an incandescent light source (C) behind a diffusing screen (D). Gratings mounted in a multistimulus projector (M) were flashed (F) through the right channel. From Towle et al. (in prep.).

size- and orientation-specific suppression and to investigate the interaction between them. Both interocular and intraocular suppression were investigated to assess the contribution of peripheral and central mechanisms to such effects. In the interocular suppression conditions, the left eye continuously viewed either the 9V, 9H, 36V or 36H gratings (presented in counterbalanced order) while VEPs were obtained to the 9V or 36H grating flashed to the right eye. In the intraocular suppression conditions, both the flashed and continuously presented gratings were presented to the right eye. Diffuse flashes were randomly intermixed among the sixty-four flashed gratings. The subject's task was to give selectively an RT response to the flashed gratings and not to the diffuse flashes. Performance was measured in terms of d' . If the subject did not respond within 375 msec poststimulus, negative feedback was presented in the form of a "click". Six subjects participated in Experiment A.

Experiment B was an investigation of the effects of directing the subject's attention selectively toward either the 9V, 9H, 36V or 36H grating while recording VEPs to the 9V and 36H flashed gratings. This experiment was identical to Experiment A with the following exceptions: 1) both eyes continuously viewed diffuse light; 2) the four different gratings were flashed in a random sequence until both the 9V and 36H gratings had been flashed sixty-four times; 3) the subject's task was to selectively give an RT

response to the attended or relevant grating and to withhold responses to the other three gratings. A negative feedback "click" was given if the subject did not respond within 375 msec following the relevant grating. The percentage of RT responses to all four stimuli were recorded, and once again a signal detection criterion was used with d' measuring how selectively subjects were responding to the relevant grating. Eight subjects participated in this experiment.

The changes in VEP amplitude as a function of the experimental conditions of both experiments were quantified by measuring amplitude at fixed or relatively fixed points in time after stimulation, in reference to a baseline (average voltage level of the first 45 msec). For Experiment A, these latencies were 75 msec, 100 msec, 125 msec, a negative peak between 125-195 msec (N150), a positive peak between 200-250 msec (P230), 275 msec, a positive peak between 280-380 msec (P320) and 425 msec. For Experiment B these latencies were 75, 125, 175, 200, 225, 250 and 375 msec. These latencies were selected either on the basis of measures used in previous studies, the peaks and troughs of the raw VEP waveform or the peaks and troughs of the difference potentials. These measures were analyzed statistically with repeated measures analyses of variance, and individual means were compared with either Newman-Keuls or Dunnett multiple range tests.

Results

The psychophysical (d') data of Experiment A indicated subjects had more difficulty discriminating the grating from diffuse flashes when the 9V, as compared to the 36H, grating was flashed ($p < .01$). The suppressing effects of the other three continuous gratings and the effects due to intra- vs interocular presentation of the continuous stimulus did not differ significantly.

The d' values obtained in Experiment B indicated the four gratings differed in terms of how selectively subjects could respond to them ($p < .01$). The highest to lowest d' values were associated with attending to the 36V, 36H, 9V and 9H gratings, respectively. A greater number of false alarms were made to irrelevant stimuli of the same size, as compared to the same orientation, as the relevant grating.

The results will be represented in the form of difference potentials (bottom Fig. 2 and Fig. 3) which reflect the change in VEP amplitude and/or latency due to reducing the number of features of the continuous or relevant grating identical to those of the flashed grating. Any significant deviation from a flat difference potential indicates the change in the continuous or relevant grating influenced

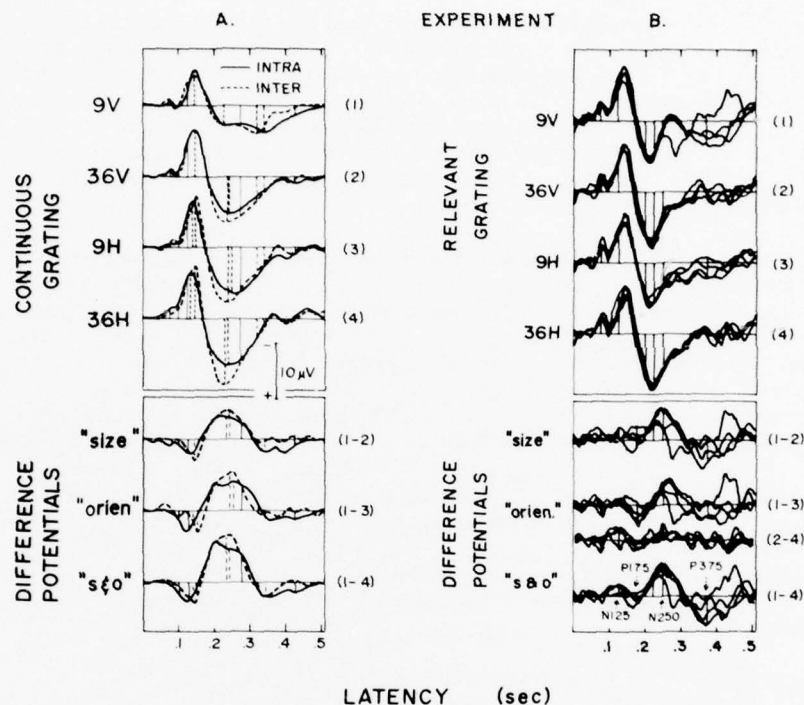


Fig. 2. VEPs (top) and difference potentials (bottom) to the 9V flashed grating. Subject MRH. Amplitude measures were made at peaks and troughs of raw data (vertical dashed lines) and at fixed latencies (vertical solid lines). Left. (Experiment A) Effects of a continuous grating upon VEPs to the flashed grating when the two gratings were viewed by the same eye (intraocular condition) or different eyes (interocular condition). Right. (Experiment B) Effects of attending one of the four gratings on VEPs to the 9V grating. The difference potentials indicate the change in VEPs when one or more features of the continuous or relevant (attended) grating were made identical to those of the flashed grating. The numbers (9 and 36) and letters (V and H) indicate the bar width (min) and orientation of the gratings.

the VEP to the flashed grating. Only VEPs to the 9V grating will be discussed in the present paper. The VEPs to the 36H gratings (Towle et al., in prep.) confirm that the effects to be discussed were feature- or pattern-specific, unless otherwise stated.

The results of Experiment A (left column Fig. 2) indicated the time course of the effects of the continuous grating on VEPs to the flashed grating was similar for both the inter- and intraocular conditions, except that intraocular suppression was greater 100-150 msec post stimulus ($p < .05$). The grouped data, averaged across the intra- and interocular suppression conditions, are shown in Fig. 3 (last column).

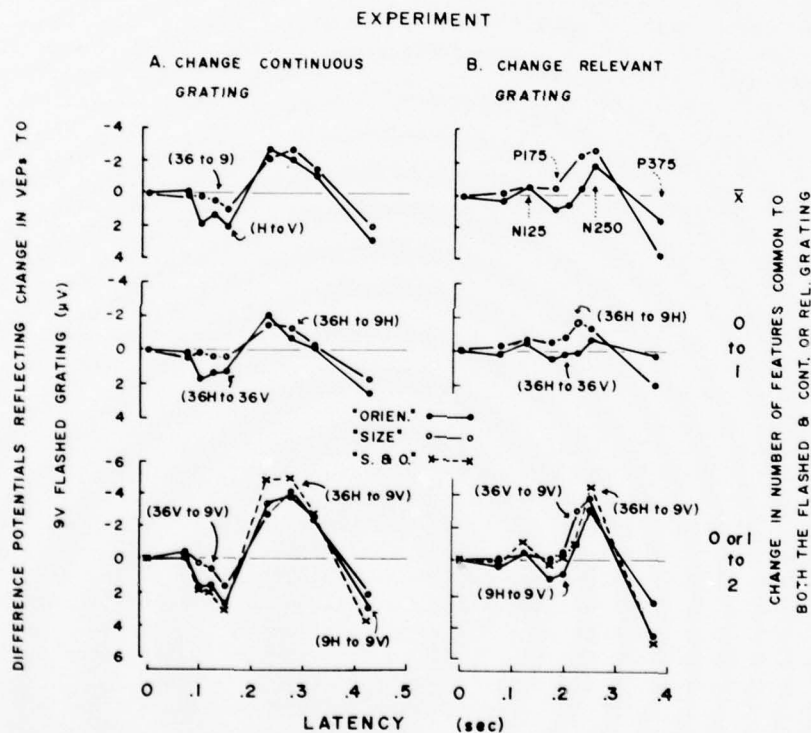


Fig. 3. Quantified difference potentials averaged across subjects and replication indicating the change in VEP amplitude due to making a feature of the continuous grating (Experiment A) or relevant grating (Experiment B) identical to that of the 9V flashed grating. Top row are the means (X) reflecting the effects of a change from 0 to 1 and from 1 to 2 features in common. Nine and 36 followed by V and H indicate the bar width (min) and orientation of the gratings.

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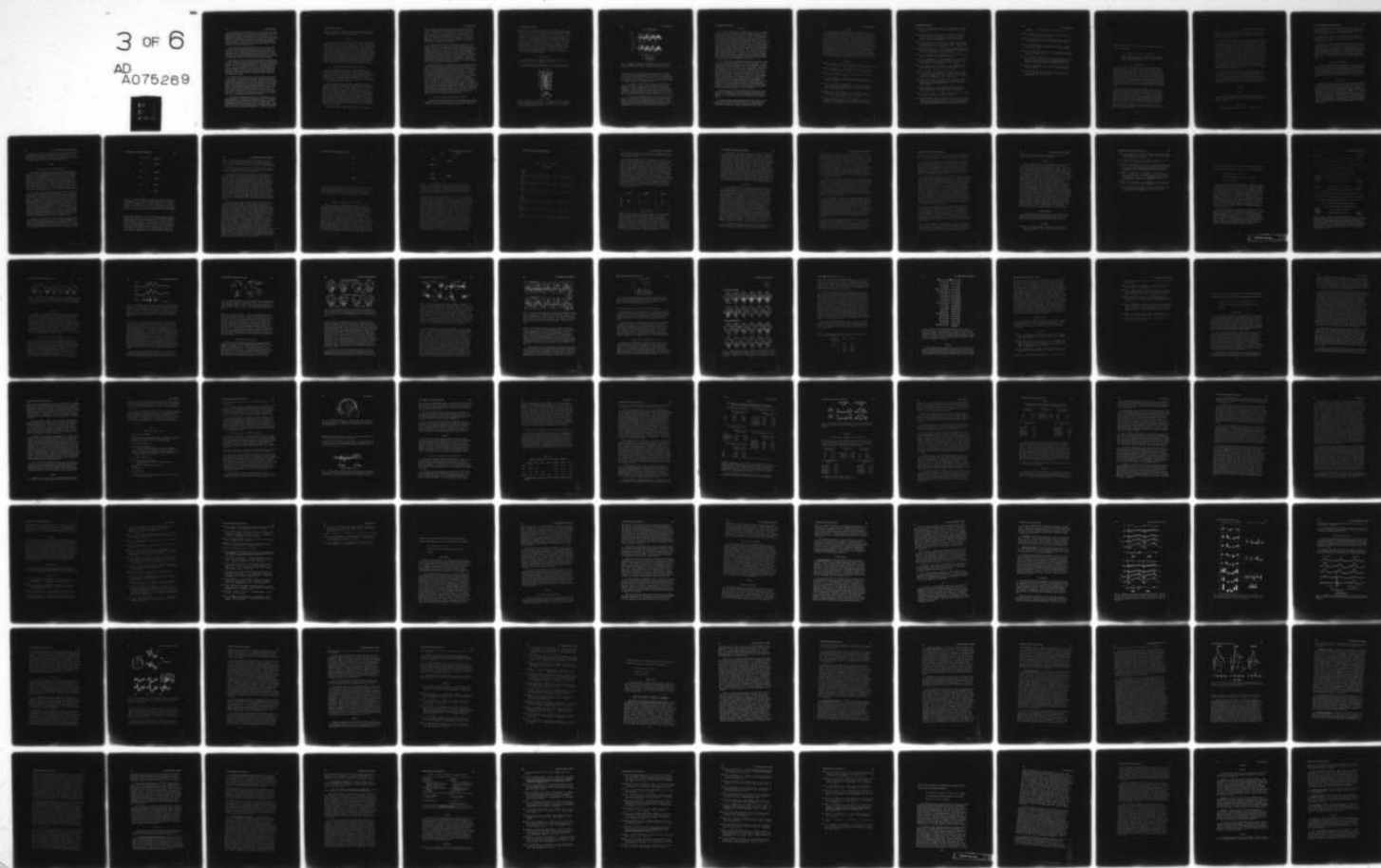
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The changes in VEP amplitude from 100 to 150 msec poststimulus indicated the following: a) greater orientation-specific than size-specific suppression; b) orientation-specific suppression was independent of spatial frequency--that is, the VEP to the 9V flashed grating was suppressed by changing the continuous gratings from 36H to 36V; c) spatial frequency-specific suppression was dependent upon orientation--that is, the VEPs to the 9V flashed grating were suppressed only by changing the continuous grating from 36V to 9V and not by the change from 36H to 9H.

After about 150 msec poststimulus, the nature of suppression to both bar size and orientation was similar. The two types of suppression were of about the same magnitude and were reflected by a negative shift in amplitude between 150 and 350 msec, followed by a positive shift in amplitude between 350 and 450 msec. At all latencies, the suppression effects were greatest when the continuous grating had both features in common with the flashed grating.

The results of the selective attention experiment (Experiment B, right column Figs. 2 and 3) indicated that which grating was task relevant influenced VEP amplitude to the 9V grating, as measured 125, 200, 225, 250 and 375 msec poststimulus ($p < .01$ except 200 msec where $p < .05$). The change in VEPs to the 9V flashed grating, due to increasing the relevance of this grating, was characterized by increased negativity between 100 and 150 msec (N125), increased positivity between 150 and 200 msec (P175), increased negativity between 200 and 300 msec (N250) and increased positivity between 200 and 400 msec (P350).

The effect of task relevance on N125 is of particular interest in that such an early effect has not been reported in response to visual stimuli in the previous literature. The influence of selective attention was evident only when the orientation of the relevant stimulus was identical to that of the flashed grating (9V and 36V) and was fairly independent of the spatial frequency of the relevant grating. The average difference potentials reflecting this orientation attention effect (solid line top-right Fig. 3)--that is, the increased negativity from 75 to 125 and positivity from 125 to 175 msec--were statistically significant ($p < .025$ and $< .01$, respectively). It should be noted that this effect was not evident in VEPs to the 36H flashed gratings (data not shown).

In general the changes in N250 and P375 in Experiment B indicated considerable interdependence between the effects of the size and orientation of the flashed and attended gratings. The effects of attending a grating with only one feature in common with the flashed grating had little influence upon the VEP amplitude. There was a small effect of this type only when the flashed and attended grating were of the same spatial frequency. A shift in attention

had the greatest effect when it was from a grating with neither feature in common to a grating with both features in common with the flashed grating (i.e., from 36H to 9V).

DISCUSSION

The results will be discussed in regards to two interrelated questions: What is the sequence in which the spatial frequency and orientation of a pattern is processed, both in terms of the neural representation of the pattern (presumably in sensory information channels) and the effects of selective attention to the pattern? And secondly, to what extent may the effects of selective attention be related to the nature of activity in sensory information channels? The series of studies reported above will be related to these two questions by first summarizing how the changes in sensory channels (induced by sensory suppression) and changes in attention (induced by task relevance) affect the VEP. Then the interrelationship of activity in sensory channels and mechanisms of selective attention will be assessed by comparing these suppression and attention effects both in terms of their time course and their specificity.

Early VEP Components and Sensory Channels

For the purposes of discussion it will be assumed that VEP components earlier than 200 msec poststimulus reflect sensory activity and/or activity not directly associated with motor processes. This assumption is based on the fact the VEP components occurring earlier than 200 msec poststimulus are influenced by stimulus parameters per se in passive subjects (Harter et al., 1976; Harter et al., in prep.) and that RT latency is typically greater than 300 msec poststimulus in a choice RT task.

The size- and orientation-specific suppression of early VEP components obtained in Experiment A may be interpreted within the framework of feature-specific neural channels (Harter et al., 1976; Harter, 1977; Towle et al., in prep.; Harter et al., in prep.). The continuously presented grating is presumed to activate and saturate those feature channels selectively sensitive to the features of the continuous grating. The response to a flashed grating with similar features would, therefore, be suppressed since this response would be mediated by the saturated channel. The response to a flashed grating with different features than the continuous grating would not be suppressed, because these different features would be processed in different neural channels. The interocular transfer of the suppression effects indicates they are mediated by cortical neural channels.

Two findings support Campbell and Maffei's (1971) suggestion

that orientation channels may precede spatial frequency channels. First, orientation-specific suppression was greater in magnitude earlier in time (100 msec poststimulus) than size-specific suppression. And second, orientation-specific suppression was, in part, independent of spatial frequency or bar width. Maffei and Fiorentini (1977) have proposed a cortical model of spatial frequency rows and orientation columns which provides one possible explanation of the difference between orientation and spatial frequency effects obtained in Experiment A.

It should be noted, however, that Smith and Jeffreys (1978) reported that the CI (75 msec) component was suppressed by both spatial frequency and orientation. This may bring the above interpretation into question. Their study differed from Experiment A in a number of respects in that they: a) used a masking paradigm, b) stimulated different portions of the visual field and recorded from different electrode positions, c) did not compare the magnitude of the effects of spatial frequency and orientation on CI; d) reported that gratings did not elicit a CII component (a component comparable to the 100 msec measure in Experiment A). These differences make it difficult to compare directly the spatial frequency and orientation effects in the two studies.

Selective attention to a grating of the same orientation as the flashed grating (9V or 36V) caused an increase in negativity of the VEP to the 9V flashed grating between 100 and 150 msec (N125). A number of factors indicate this effect might reflect the modulation of activity in orientation-specific sensory channels. First, the latency and polarity of N125 is comparable to that of the effects of pattern per se (Harter and Previc, 1978, and others). Second the continuous orientation suppression in Experiment A was reflected in increased positivity between 100 and 150 msec poststimulus which is as expected since suppression effects are presumably of opposite polarity as the facilitory effect due to selective attention. Finally it is unlikely that differential states of preparation for the relevant and irrelevant gratings can account for the N125 effect since these gratings were presented randomly. The N125 effect adds to previous data which indicate selective attention influences the amplitude of sensory VEPs (Eason et al., 1969; Harter and Salmon, 1972; Van Voorhis and Hillyard, 1977; Harter and Previc, 1978). It should be noted that this N125 attention effect appears to be uniquely related to attending vertical gratings.

Late VEP Components and Cognitive Processes

The negativity peaking at about 250 msec and positivity peaking at about 350 msec in both Experiments A and B may be attributed to cognitive processes related to performing the RT task. These late

effects have not been reported in previous studies of suppression where the subjects were not required to discriminate stimuli (Harter et al., 1976; Harter, 1977; Smith and Jeffreys 1978; Harter et al., in prep.). In the case of Experiment A it is not clear just what cognitive processes might account for the change in amplitude of N250 and P350. The components have been attributed to either task relevance or subjective probabilities of stimuli (Donchin et al., in press). Yet in Experiment B these processes were not applicable since the evoking 9V grating was always task relevant and of the same probability (.5) as the irrelevant diffuse flashes. Visual inspection of the raw VEPs indicate the changes in N250 amplitude cannot be related to changes in latency of this component. Most likely these later components may be attributed to changes in difficulty in performing the choice RT task due to the suppressing effect of the continuous stimulus.

APPLICATIONS

Eliminary data on the potential applications of the above procedures may be briefly summarized as follows:

1. Estimation of perceptual acuity. Towle and Harter (1977) reported that the smallest pattern element size that would elicit

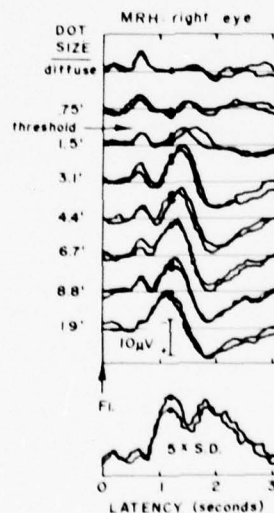


Fig. 4. Example of how differences in diffuse and pattern VEPs may be used to estimate visual acuity. The smallest dot-size eliciting a pattern VEP was 1.5' and was the smallest dot-size perceptible. Data from Towle and Harter (1977).

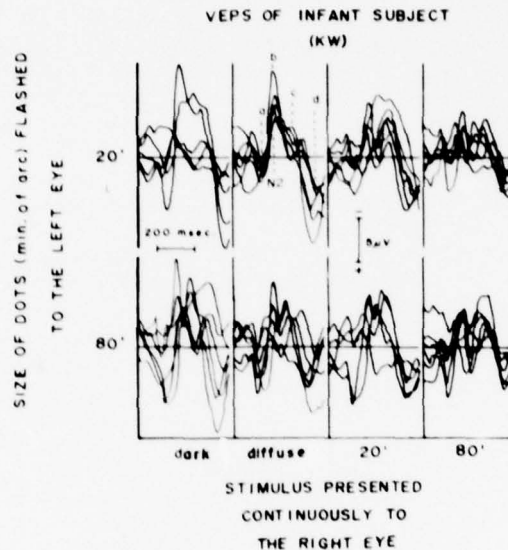


Fig. 5. Example of interocular suppression of VEPs in an infant due to the presence and size of pattern in the contraocularly presented continuous stimulus. From Odom and Harter (in prep.).

a pattern VEP--the VEP pattern threshold--was highly correlated ($r=.89$) with perceptual measures of visual acuity. Perceptual acuity could be estimated to within plus or minus .29 decimal units on the basis of VEPs (Fig. 4). Harter et al. (1977a,b) and others (see review by Dobson and Teller, in prep.) have used pattern VEPs to estimate visual acuity in human infants.

2. Estimation of binocularity and depth perception ability. Harter et al. (1977c) found greater size-specific interocular suppression of VEPs in subjects with good stereopsis and depth perception. Odom and Harter (in prep.) used the color separation (anaglyphic) method to demonstrate interocular suppression of pattern VEPs in human infants (20-112 days of age) (Fig. 5). These results indicate human infants have some degree of binocular vision.

3. VEP selective attention effects in learning disabled children. Musso and Harter (in press) reported that the effects of selective attention on VEP amplitude (N200 to P300) were significantly greater in reading disabled than normal children. This finding was interpreted as indicating reading disabled children were compensating for a deficit in processing visual information.

CONCLUSION

The studies summarized here investigated how the visual system extracts, processes and selects relevant features from the visual image--specifically the features of size (spatial frequency) and orientation. Two types of paradigms were used in these studies. The first isolated feature-specific sensory channels by assessing the effects of continuously presented suppressing gratings on VEPs to a flashed grating. These studies demonstrated interocular suppression due to both spatial frequency and orientation. This suggests that such suppression is partially mediated by binocular cortical channels. The nature of feature-specific suppression of the early VEP components (100-200 msec poststimulus) was interpreted as indicating that orientation channels may be activated before size channels and are initially independent of size channels. In contrast, spatial frequency and orientation effects did not closely parallel the behavioral measure of suppression. Suppression of the later components (200-400 msec poststimulus) indicated size and orientation effects were approximately the same magnitude, were interdependent and were related to the behavioral measure of suppression.

The second experimental paradigm employed was designed to assess the effects of selective attention to a particular pattern on VEPs to patterns varying orthogonally in size and orientation. Of particular interest was the finding that an early component (N125) was influenced by selective attention. This early effect could reflect the modulation of activity in orientation channels since it was orientation-specific. Yet since it was reflected in VEPs to the 36H grating when it was selectively attended, the origin of this component is uncertain. The effects of attention on later components (N250 and P357) (a) were specific to the size and orientation of the relevant grating, (b) were greater when the relevant and flashed grating had the same spatial frequency as compared to orientation and (c) indicated considerable interdependence of the processing of size and orientation as did the behavioral data. The changes in the later components appeared to reflect differential processing of information prior to initiation of the motor response but did not appear to reflect directly the modulation of activity in the earliest feature-specific sensory channels.

The time course of both the suppression and attention effects upon the VEPs reflected a temporal progression from relative independence to interdependence of spatial frequency and orientation channels (i.e., from feature-specific to pattern-specific processing).

Preliminary data were presented reflecting the potential application of these VEP measures as correlates of visual acuity and binocularity in adult and infant subjects and as correlates of attentional differences in reading disabled and normal children.

SUMMARY

Visual evoked potentials were used to investigate the processing of information in spatial frequency and orientation channels. Intra- and interocular suppression of early VEP components (100-200 msec poststimulus) indicated that there are spatial frequency and orientation channels and that orientation channels are activated before spatial frequency channels. Suppression of later VEP components (200-400 msec poststimulus) indicated an additional type of channel which was spatial frequency- and orientation-specific, and which appeared to mediate the specificity of the behavioral measure of suppression. The effects of selective attention to a given grating on VEP amplitudes were specific to the size and orientation of the relevant grating. These effects appeared to be mediated by the modulation of activity in cortical sensory channels. The time course of both the suppression and attention effects on VEP reflected a progressive increase in the specificity of information channels - from feature-specific to pattern-specific - up to that point in time when the behavioral response was initiated.

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MATURATION AND TASK SPECIFICITY OF CORTICAL POTENTIALS ASSOCIATED
WITH VISUAL SCANNING

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INTRODUCTION

During normal vision the world is continuously scanned by a sequence of saccadic eye movements that shift the direction of gaze from two to six times each second. When viewing a stationary field, perceptual information is derived from the retinal images formed during fixational pauses. Eye position during fixation determines the portion of the visual scene that is available for processing and the duration of each fixation defines the time required for processing that information before the next saccade. Thus, the recording of eye movements provides an objective behavioral index of visual processing. Since visual scanning behavior is observed in the alert human subject from birth, oculomotor behavior provides a unique index of visual processing that can be observed throughout life.

It has been shown, both in free scanning and in controlled visual search tasks, that fixation duration (or intersaccade interval*) increases with field and task complexity (e.g., Gould and Schaffer, 1967; Gould and Peeples, 1970). Mean fixation duration also varies with age, progressively decreasing during childhood. There is a differential effect of task variables on these maturational changes, with the adult fixation duration being achieved by six years for picture scanning (Mackworth and Bruner, 1970), but not until 12-14 years of age for reading and numerical processing

*5% or less of visual scanning time is occupied by saccades, so that measurement of intersaccade interval provides a close approximation to fixation duration.

(Gilbert, 1953). Thus, visual processing time as indexed by measurement of intersaccade interval shows both maturational and task related variations that can in part be related to efficiency of visual information processing.

Recordings of brain potentials concurrent with visual scanning provide a direct probe of the cortical mechanisms underlying vision. By averaging cortical activity in synchrony with saccades, eye movement potentials (EMP) are recorded that both precede and follow the eye movements. The antecedent potentials consist of activity that begins approximately 200 msec before eye movement onset, culminating in a sharp positive deflection that peaks during the saccade. These potentials are maximum in amplitude over the posterior parietal and posterior frontal regions and are presumably implicated in the programming and initiation of saccades. The potentials that follow the eye movements, designated the lambda complex, are largest over the occipital region and vary in morphology and timing as a function of field characteristics and eye movement size. As the amplitude and duration of voluntary saccades are progressively increased, distinct components that are temporally related to saccade onset and to the subsequent fixational pause, become increasingly differentiated. For eye movements less than 10° in amplitude, however, the lambda complex comprises a composite of overlapping saccadic and fixational components (Kurtzberg and Vaughan, 1977).

The recording of eye movements and the associated EMP during visual scanning provide behavioral and electrophysiologic indices of visual processing that could provide valuable information on normal and deviant perceptual and cognitive development. In order to assess the potential value of these methods in developmental studies of vision, we have surveyed the maturational changes in EMP and fixation duration from birth to adulthood and have examined task related differences in these measures in school-age children and adults.

METHODS

Subjects

Thirty infants ranging from 34 weeks post-conception to 10 months of age, ten children 4 to 16 years of age and eight adults from 20 to 48 years were studied. All of the children and adults were right handed.

Visual Stimuli

The scanning targets differed with the age of the subject.

For preterm, newborn, and young infants, the targets were black and white patterns (e.g., bullseye, schematic face) which elicit robust scanning behavior. Older infants were shown simple colorful pictures of animals mounted on a white background.

For preschool children, pictures were taken from children's books that depicted events in the schoolroom, at a train station, at the circus, etc. All of these materials subtended a total visual angle of 30-40°.

School-age children and adults were presented with three kinds of visual stimuli: 1) museum reproductions of paintings; this condition was analogous to the target and picture scanning of the younger children. 2) pencil mazes; this was considered to be a non-verbal, purely spatial task. 3) reading selections taken from the Houghton-Mifflin reading program; children were given selections to read from their grade level and from lower and higher grades as well; adults were given selections from 6 grade levels (2, 4, 6, 7, 8, 9). These stimuli subtended visual angles between 20 and 40°.

Recording Procedures

EEG was recorded from electrodes placed at O1,2; T5,6; P3,4; C3,4; and F3,4 referred to the linked ears. Horizontal and vertical EOG were recorded from electrodes placed at the outer canthi of both eyes, and above and below the orbit of one eye. EEG and EOG were recorded on a Model 6, Grass EEG machine, with system gain of 10K and frequency response down 3dB at 1 and 70 Hz. The electrophysiologic signals were recorded on a 14-track FM tape recorder.

Data Analysis

The data were digitized off-line by a Nicolet Med 80 computer programmed to average from the onset of each saccade over a specified epoch before and after each eye movement. The computer was set to reject epochs in which potentials exceeded a designated voltage so as to exclude blinks and other artifacts from the averaged EMP. EMP were averaged for each task separately and contained a minimum of 150 epochs. The averaged EMP were written out on an XY plotter. Peaks were identified visually and designated by polarity and peak latency. The duration of the principal lambda potential was also measured. This component was usually clearly defined in the occipital recordings either by a sharp departure and return to the baseline or by small negative peaks that preceded and followed it.

Intersaccade interval distributions for each task were obtained by measurements taken directly from the paper record. Intervals bounded by or interrupted by blinks or other artifacts were rejected. Mean intersaccade intervals were calculated and intersaccade interval histograms were constructed for each scanning task.

RESULTS

Maturation of Eye Movement Potentials

In the normal full term infant, brain potentials associated with the scanning of patterns precede and follow the eye movements (Figure 1A). The lambda response consists of a relatively simple positive wave most prominent over the occipital region, with mean peak latency from eye movement onset of 279 ± 60 msec and a mean duration of 259 ± 82 msec. The individual differences in the temporal characteristics of the lambda response are paralleled by variations in mean intersaccade interval. Mean intersaccade interval for these infants is 504 ± 65 msec. Pairwise correlation between lambda duration and mean intersaccade interval across infants is .87 ($p < .005$), indicating a close relationship between the behavioral and electrophysiological indices of visual processing time.

In premature infants, scanning of black and white targets was observed as early as 34 weeks post-conceptual age (i.e., 2 months before term). In these babies, the periods of active scanning are brief and the associated cortical potentials are often poorly defined. As infants approach term (i.e., 40 weeks post-conceptual age), scanning behavior is more consistently elicited. The eye movement potentials of the premature infants at term display similar morphology to that recorded from the full term infant but differ in the temporal characteristics of the lambda response. The mean peak latency of the lambda wave in the preterm infants is 437 ± 135 msec, and lambda duration is 353 ± 177 msec. The mean intersaccade interval for the group is 530 ± 74 msec. All of these measures of visual processing time are longer in the premature infant at 40 weeks than the full term baby at the same age. The correlation between mean intersaccade interval and lambda duration, .73 ($p < .025$), is somewhat lower than in the full term infants.

During the first four to six months of life, the lambda potential is similar in waveform to that of the newborn (Figure 1B, 1C) but the large positive component peaks at progressively shorter latencies, being reduced to 200 msec by six months of age. Around this time, the potentials become more complex (Figure 1C) and except for a systematic decrease in latency with age, are similar in wave-

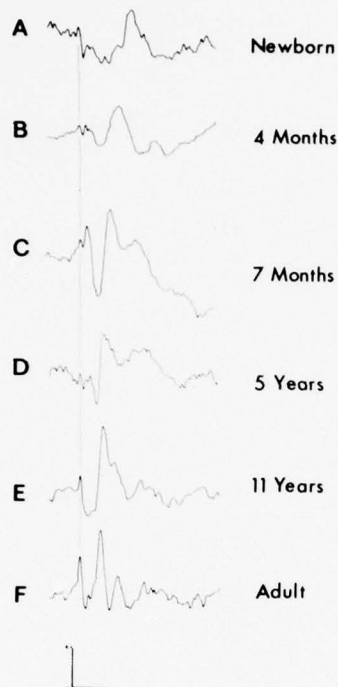


Figure 1. Eye movement potentials associated with pattern or picture scanning in (A) a newborn (N=225); (B) 4 month old (N=400); (C) 7 month old (N=260); (D) 5 year old (N=384); (E) 11 year old (N=185); and (F) adult (N=242). Dotted line indicates eye movement onset. Recording site: occipital. Calibration: 10 uV for A-E and 5 uV for F; 200 msec. Note the progressively shorter peak latency of the prominent positive lambda potential with maturation.

shape to the potentials associated with picture scanning in children and adults (Figure 1D, E and F). The lambda complex comprises a small negativity at 20-30 msec followed by a series of small and variable positive wavelets at 35-80 msec seen at these latencies both in children and adults. There is however, a decrease in latency of the later components from children to adults. A negative wave peaks at a mean latency of 89 ± 15 msec for the children and 79 ± 14 msec for the adults and is followed by a positivity at 141 ± 24 msec (children) and 121 ± 11 msec (adults). These negative and positive components are the largest and most consistent

portions of the lambda complex during picture scanning. Later components are smaller and more variable: a negativity peaking at 256 ± 76 msec (children) and 186 ± 20 msec (adults), followed by a positive wave at 403 ± 59 msec (children) and 239 ± 13 msec (adults).

The duration of the main positive wave of the lambda complex differs substantially between the children and adults, being 201 ± 59 msec in children and 108 ± 17 msec in adults.

Although the mean intersaccade interval is substantially reduced in children and adults as compared to the values observed in the infant subjects, the relation of lambda response latency and duration to mean intersaccade interval differs across these age groups. Whereas the lambda wave duration is reduced by an average value of 58 msec between the infants and children and a further 93 msec between the children and adults, the mean intersaccade interval diminishes 220 msec from infants to children (504 to 284 ± 28 msec), but the adult mean intersaccade interval (298 ± 31 msec) does not change significantly from the children's value. Despite this discrepancy across age groups, the correlations between lambda duration within each group remains fairly high, $.78$ ($p < .005$) for children and $.68$ ($p < .05$) for adults. These findings indicate that the duration of the occipital lambda wave, while related to processing time as indexed by the mean intersaccade interval, does not fully depict the mechanisms underlying the determination of fixation duration.

The foregoing description of maturational changes applies to the occipital lambda response. EMP are also recorded over other portions of the scalp, usually at lower amplitude and most consistently in the posterior temporal and parietal regions (Figure 2). Some of the temporoparietal activity possesses the same latency and waveshape as the occipital response but is generally smaller. These potentials are considered to be volume conducted from the occipital cortex. Other activity is seen at longer latencies than the corresponding occipital components. Distinct differences in the timing of temporal and parietal potentials are seen principally in components that peak more than 80 msec after eye movement onset and the largest difference is in the main positive wave that peaks between 125 and 200 msec in the children and adults and the negativity that follows it between 200 and 300 msec. During the first few months of life, distinct temporoparietal potentials are inconstant. After six months, however, prolonged posterior temporal potentials become evident that are also prominent in the younger children. Most of the school-age children and adults show a sequence of temporal and parietal potentials that differ in latency from the occipital lambda response. In children and adults, the largest positive lambda component is 50 msec longer in latency in the temporal region on the average, than in the occipital region. The parietal positive wave lags the occipital by an average of only 10 msec.

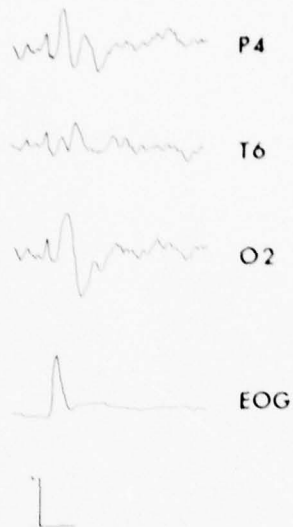


Figure 2. Eye movement potentials associated with picture scanning recorded from an adult subject. $N=280$. Calibration: 5 μV , 200 msec. Note the prominent positive lambda potential recorded at maximum amplitude over the occipital region. Potentials that differ in timing are also seen at both the parietal and temporal sites.

EMP During Reading and Maze Tracing

EMP recorded during reading and maze tracing in school-age children and adults differ in morphology and temporal characteristics from those recorded during picture scanning. Typical waveforms for the reading and maze conditions recorded from the right and left occipital and temporal electrodes are depicted in Figure 3 for one subject. It can be seen that there are differences in the timing of both the occipital and temporal lambda components in the two tasks. In general, the components are longer in duration or latency in the maze task as compared to reading. The peak latencies of the occipital and temporal lambda components are summarized in Table 1. Latency differences between occipital and parietal components are small. In each condition, latencies for all but the first two lambda components are longer in children than in adults. With only one exception, the latencies are greater for picture scanning and maze tracing than for reading. Occipital lambda wave duration also manifests similar changes, being briefer in the adults for all conditions and shortest for reading in both age groups. Inter-

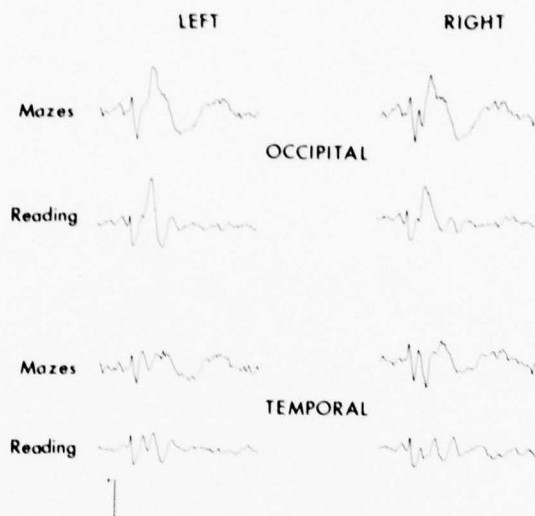


Figure 3. Eye movement potentials associated with maze tracing (N=290) and reading (N=432) recorded from an 11 year old child. Calibration: 10 μ V, 200 msec. Note the shorter latencies of the potentials associated with reading compared with those recorded during maze tracing and the relative amplitude differences between the occipital and temporal electrode pairs for the two tasks.

saccade intervals show similar effects of task, but are essentially the same within each task across age groups. It should be recalled that this reduction in lambda wave duration without a corresponding decrease in intersaccade interval was also found between the children and adults in picture scanning. In that condition, however, the correlations between lambda duration and intersaccade interval within each age group were substantial, $r=.78$ for children and $r=.68$ for adults. In reading the correlations were smaller, $.51$ in children and $.42$ in adults. No relationship between occipital lambda duration and intersaccade interval was found ($r=.25$ for children and $r=.15$ for adults) in the maze tracing tasks. It appears, therefore, that the occipital lambda duration is most closely related to intersaccade interval in picture scanning. The potentials recorded in the temporal region appear to show a relationship to fixation duration in reading and maze tracing inasmuch as the mean differences in intersaccade interval between these tasks are similar to the differences in mean peak latency of the late positive temporal lambda components. Furthermore, in reading the intragroup correlations between the temporal lambda peak latency and intersaccade interval are substantial, being $.75$ ($p<.005$) for children and $.65$ ($p<.005$) for adults. However, the correlations for maze tracing are relatively low: $.16$ for children and $.48$ for adults. The

Table 1. Latency of EMP peaks.

LATENCY SUMMARY						
	N	P	N	P	N	P
<u>OCCIPITAL</u>						
<u>Pictures</u>						
Children	21 ± 4	32 ± 4 / 68 ± 5	89 ± 15	141 ± 24	256 ± 76	403 ± 59
Adults	28 ± 9	36 ± 11 / 65 ± 13	79 ± 14	121 ± 11	186 ± 20	239 ± 13
<u>Mazes</u>						
Children	26 ± 5	40 ± 6 / 68 ± 4	84 ± 10	130 ± 14	274 ± 26	385 ± 74
Adults	28 ± 7	41 ± 10 / 70 ± 7	77 ± 16	111 ± 11	170 ± 21	224 ± 36
<u>Reading</u>						
Children	25 ± 5	39 ± 10 / 69 ± 18	81 ± 17	122 ± 13	225 ± 24	300 ± 55
Adults	22 ± 5	34 ± 8 / 60 ± 9	70 ± 15	109 ± 12	168 ± 22	234 ± 38
<u>TEMPORAL</u>						
<u>Pictures</u>						
Children	26 ± 11	27 ± 6 / 68 ± 12	105 ± 10	199 ± 25	288 ± 21	390 ± 70
Adults	20 ± 0	35 ± 8 / 66 ± 13	95 ± 13	128 ± 8 / 174 ± 33	195 ± 7	
<u>Mazes</u>						
Children	26 ± 5	38 ± 10 / 77 ± 18	112 ± 16	166 ± 42 / 225 ± 64	330 ± 27	453 ± 75
Adults	23 ± 7	33 ± 8 / 72 ± 8	99 ± 10	130 ± 12 / 203 ± 23	260 ± 14	
<u>Reading</u>						
Children	24 ± 8	60 ± 14	92 ± 21	126 ± 26 / 172 ± 25	248 ± 40	324 ± 63
Adults	20 ± 0	35 ± 8 / 69 ± 8	89 ± 8	118 ± 13 / 150 ± 22	180 ± 10	222 ± 36

only significant correlation between parietal lambda peak latency and intersaccade interval, $r=.68$ ($p<.005$), was found in the adult subjects during reading.

In order to assess possible interhemispherical differences in amplitude of the lambda response in relation to the verbal or non-verbal nature of the visual task, amplitude ratios for the main positive lambda component were computed between homologous electrode pairs in each stimulus condition. There was a small mean right hemispherical amplitude preponderance for the maze task in the occipital, posterior temporal and parietal lambda for both children and adults. Among the fifteen individual subjects for whom interhemispherical ratios were calculated, ten manifest a right sided lambda preponderance at the occipital and parietal sites and nine at the posterior temporal. Two subjects at the parietal and one at the occipital and temporal electrodes show no interhemispherical asymmetry, whereas the remaining subjects have responses that are larger on the left side. During reading, by contrast, ten subjects show a left occipital preponderance, thirteen a left temporal preponderance, but only in eight is the left parietal response larger than the right. A particularly instructive comparison between the tasks is depicted in Figure 4.

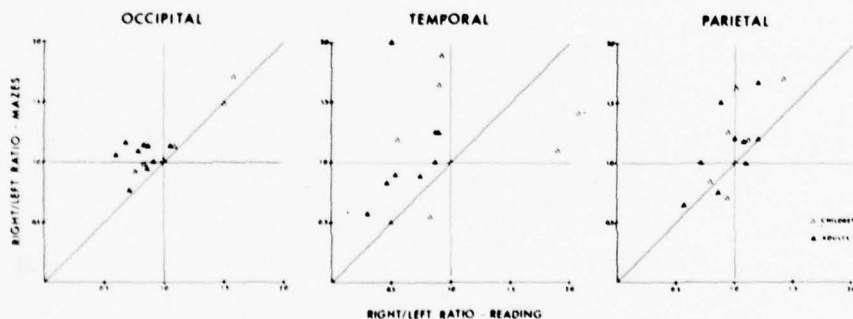


Figure 4. Scatterplots depicting the right-left ratios of lambda potential amplitude for the occipital, temporal and parietal electrode pairs in maze tracing and reading. The dotted lines represent ratios of 1 which indicate no amplitude asymmetry. Points to the left of 1.0 on the abscissa represent subjects who displayed a left-sided predominance during reading. Points above 1.0 on the ordinate are subjects who showed a right-sided preponderance for maze tracing. The diagonal line represents equal interhemispherical ratios for each task. Points above and to the left indicate a left-sided shift in amplitude for reading compared with maze tracing; below the line, a right-sided shift.

In the graph, the subjects who manifest a shift toward amplitude ratios favoring the left hemisphere for reading as contrasted to maze tracing, appear above and to the left of the diagonal. At the occipital electrode, only one subject, a six year old child, fails to show change in amplitude ratio favoring the left hemisphere during reading. At the temporal site, the three youngest subjects shift toward the right, an eight year old shows no shift, whereas the children over eight years of age and all of the adults shift toward the left. The amplitude ratios at the parietal location also shift to the left during reading in eleven of fifteen subjects. Here, however, two adults and one child show a right sided shift and one child shows no task related shift. These data, therefore, show a strong tendency for the occipital and parietal lambda response amplitude to manifest a relative amplitude increase in the dominant hemisphere during reading in comparison with a non-verbal task. A similar shift is seen over the posterior temporal region, but this is age related, with only the adults and older children manifesting the tendency toward relative increase in left hemispherical activity.

DISCUSSION

Before commenting on these findings, attention must be drawn to the unique features of the EMP associated with active scanning. Alone among the various event related cerebral potentials, these EMP index cortical processes that reflect the active exploration of the environment by the subject. In contrast to the repetitive presentation of brief stimuli required in conventional evoked potential recording, the changes in visual input required to elicit brain responses are produced by the saccadic shifts in eye position actively generated by the subject as he processes the information contained in a given visual scene. Although the saccadic system is partially under volitional control, the eye movements of active scanning are largely involuntary, being defined jointly by the nature of the visual field and the cognitive requirements of the viewer. With the sole exception of the rapid eye movements of paradoxical sleep, saccadic scanning occurs only in alert subjects presented with a patterned visual stimulus focused on the retina. Under these conditions scanning appears to be virtually obligatory, a fact that permits EMP to be studied in infants, young children and others who may be incapable of making reliable behavioral responses to significant stimuli. The occurrence of scanning behavior implies that visual information is being processed to the extent required to program the sequence of fixations and saccades.

It is important to recognize that the visual processing during a given fixation necessarily occupies only the time required to transmit and extract information needed to program the following

saccadic vector. This may not correspond to the total amount of time during which information of cognitive significance is derived from that fixational input. Thus, brain activity related to cognitive processing of the visual input might continue after the initiation of the succeeding saccade. An analogous situation is found with event related potentials recorded during discriminative tasks that require a motor response. Often, the response precedes the late ERP components that are presumed to reflect some aspect of cognitive processing (Ritter et al., 1972). Despite the possibility that cortical processing of input from each fixation might outlast the fixational pause, the major lambda response components were all shorter in latency than the mean intersaccade interval. This is consistent with the supposition that processing of information derived from each fixation is essentially completed before the next saccade is generated.

One objective of the present study was to evaluate the extent to which intersaccade interval is correlated with the timing of EMP components. Since it has been shown that the EMP comprises several components, some associated with saccade onset and others with onset of fixation (Kurtzberg and Vaughan, 1977), it was anticipated that the timing of some portions of the EMP would not be related to fixation duration. Furthermore, variations in the nature of the visual processing requirements would be expected not only to affect processing time, but should engage different cerebral mechanisms, so that associated variations in EMP configuration and topography are to be anticipated.

It is noteworthy that newborn infants who manifested the simplest lambda response, a single positive wave, showed the highest correlation between mean intersaccade interval and lambda duration. The strength of the relation between mean intersaccade interval and occipital lambda duration in picture scanning diminished somewhat in children and adults whose potentials manifested greater spatial and temporal complexity than the newborns. Yet, even in adults the duration of the main occipital peak accounted for approximately 50% of the variance in mean intersaccade interval across subjects. It seems reasonable to conclude, therefore, that the neural processes reflected in the principal occipital lambda component may be involved in determining the duration of fixation during picture scanning.

It is also likely that the maturational decrease in both intersaccade interval and lambda wave duration reflects increasing efficiency of visual processing with age. It is of interest that within each age group there was a considerable spread in the measures of visual processing time, indicative of substantial individual differences in efficiency of visual processing. The study of individual differences in visual scanning and EMP may prove of con-

siderable value, not only for investigating variations in visual processing in normal subjects, but also for detecting and probing the mechanisms of deviant visual processing in infants and children.

In the present investigation we found that premature infants often manifested prolonged cortical lambda potentials and mean intersaccade intervals at 40 weeks conceptional age, in comparison with normal full term newborns. In view of the fact that a number of these infants also have impaired visual orienting behavior (Kurtzberg et al., submitted for publication), analysis of the maturation of visual scanning in infants at risk for deviant neuro-behavioral development may provide a useful tool for early detection of higher visual processing disorders.

The functional correlates of task-related differences in lambda response morphology and topography remain to be established, but the present study provides some tentative indications. The high correlation between occipital lambda duration and intersaccade interval in all age groups during picture scanning, and the relatively low correlations at the occipital site for reading and maze tracing, suggest that the neural processes related to control of fixation duration are reflected in the occipital response only for picture scanning. Reading, however, is associated with enhanced temporal and parietal lambda responses that manifest a moderately high correlation between their timing and the mean intersaccade interval. It seems reasonable to conclude that these temporoparietal potentials index some aspect of the information processing specific to this task. Only maze tracing failed to show significant correlations between the behavioral and electrophysiologic indices of processing time at any of the electrode sites. Thus, cortical potentials specifically related to the control of fixation duration remain to be identified in the latter task.

Despite this failure to detect activity related to fixation duration in the spatial task, the analyses of interhemispherical differences between reading and maze tracing revealed rather consistent asymmetries in relative lambda amplitude that conformed to the presumptive lateral specialization for verbal versus non-verbal processing. These findings encourage the use of EMP recording in the investigation of lateral specialization of cortical visual mechanisms. The study of children with developmental dyslexia and other learning disorders may also be a fruitful application of these methods.

These developmental studies of EMP during active visual scanning are still in progress, incorporating improvements designed to enhance the spatial and temporal resolution of individual components that may reflect specific aspects of visual processing mechanisms. It is anticipated that these investigations will yield useful

information on cortical processes associated with normal and deviant perceptual and cognitive development.

SUMMARY

EMP associated with scanning of patterns in infants below four to six to six months of age are rather simple, with a single positive occipital lambda wave predominating. Around six months the occipital lambda potentials become more complex in form. Temporal and parietal components emerge that are distinguishable from the occipital potentials on the basis of differences in waveshape and timing. After six months, the waveform of the lambda complex undergoes little change except for systematic decreases in latency during childhood. There is a significant relation between the mean intersaccade interval and the occipital lambda duration for individual subjects within each age group, with correlations of .87 for full term infants, .78 for children and .68 for adults. Visual scanning and the associated EMP are influenced by both the characteristics of the visual field and the nature of cognitive processing requirements, intersaccade intervals increasing with field and task complexity. EMP recorded in school age children and adults during reading and the performance of non-verbal spatial tasks, manifest characteristic differences in timing and topography as a function of stimulus and task variables. The potentials recorded during reading are shorter in duration than those associated with non-verbal tasks in both children and adults. It also appears that differences in visual processing may be reflected in differential topographic features, especially in the later lambda components. There is a relative left-sided preponderance in lambda amplitude during reading as compared to a non-verbal task in right-handed subjects. This left preponderance is most marked in the posterior temporal region of adults, whereas the children's lateralization is more consistent in the occipital recordings.

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MULTICHANNEL MAPPING OF SPATIAL DISTRIBUTIONS OF SCALP POTENTIAL
FIELDS EVOKED BY CHECKERBOARD REVERSAL TO DIFFERENT RETINAL AREAS

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This paper will examine the components of potentials evoked by checkerboard reversal. The components will be defined in terms of latency and scalp location, and we will show changes of components as a function of retinal stimulus site. A considerable problem in conventional evoked potential assessment is the different potential waveshapes which are recorded from different electrode sites on the head (see Fig. 1). In addition, waveshapes at given electrode sites may change when a different reference is used. An example is shown in Fig. 1 where a set of simultaneously recorded evoked potential data from forty-seven electrodes is illustrated as waveforms using two different reference points, the mean of the ears or an anterior midline electrode (Fig. 1A and B). Of course, any one of the forty-seven channels could have been used as a reference, creating an immense number of different waveshapes out of the same data set.

However, this data set can easily be reviewed when it is presented in the simple form of a sequence of equipotential line maps which illustrate the distribution of the evoked scalp field at different times after the stimulus onset. Fig. 2 gives examples constructed from the same data as Fig. 1. The maximal response (i.e., the maximal voltage within the field) can be located in the maps quite easily. The structure of the field distributions, and thus the locations of maximal field values, is independent of a reference point; only the labelling of the equipotential lines changes with a change of reference (Lehmann, 1977).

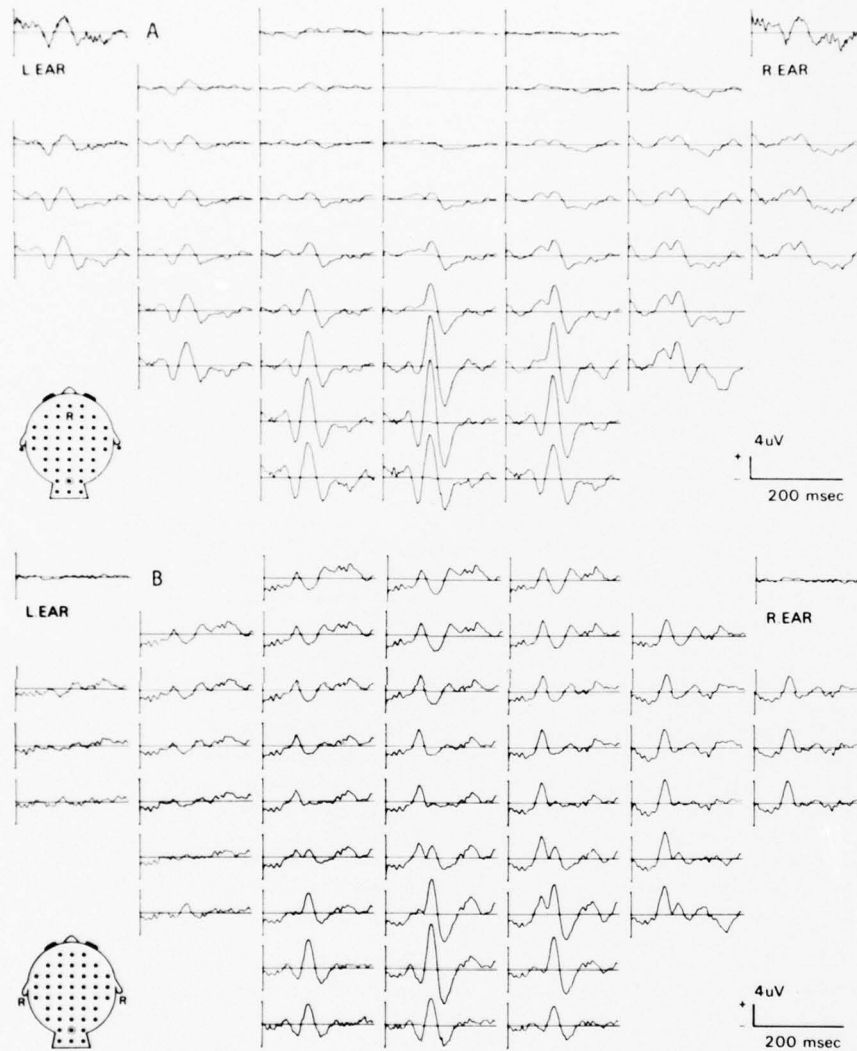


Fig. 1. Average ($N=110$) potential waveforms evoked by 2/sec checkboard reversal (circular 26° field, checks $40'$, right eye, fixation upper target edge) and recorded simultaneously from forty-seven electrodes as indicated in inset. Head seen from above, nose up, circled electrode=inion. Waveforms in A referred to an anterior midline reference (R), in B to mean of both ears. Both sets of waveforms and Fig. 2 were computed from same data set. (From Lehmann and Skrandies, in prep.)

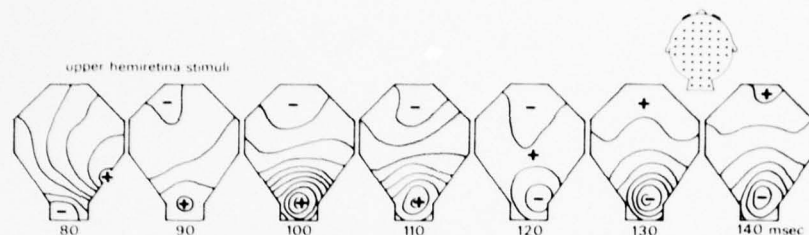


Fig. 2. Scalp field equipotential line maps, constructed from same data set as Fig. 1 (47 channel recording), for different times after stimulus reversal onset. The potential step between two adjacent lines is 1 μ V. Electrode array see inset. (From Lehmann and Skrandies, in prep.)

METHODS

All data were collected from healthy volunteers (20-45 years of age). The checkerboard (checks of 40 or 50 min arc) was back-projected as a circular field onto a translucent screen (white: 1.8 log fL, 96% contrast ratio) and reversed at 2 changes per second using a feedback controlled mirror (General Scanning CCX-101, 3 msec reversal time, no overshoot). Data were collected from Grass gold cup electrodes attached with Grass electrode cream, using up to forty-seven preamplifiers (constructed by J. Madey, 0.5 - 100 Hz at 6 dB). The data were simultaneously A/D converted at 512 s/sec/channel, stored and sequentially read via a 64 channel converter and formatter (B. Fricker, H.P. Meles and V. Crotti, Inst. Tech. Physics, ETH Zurich, and Neurology Dept., University of Zurich) and via DMA into a PDP-11/10 for further analysis.

Determination of the Time of Maximal EEG Response

It is reasonable to assume that the maximal response of the brain is reflected on the scalp as a maximal voltage difference between two recording points. Since it cannot be known in advance which two sites on the scalp will show a maximal voltage difference, all recording points must be compared. This procedure will determine two recording points at every analysis time, one for the maximal and one for the minimal voltage of the field. Using this approach, the size of the maximal voltage difference within the recorded area can be plotted as a function of time (Fig. 3B for upper hemiretina stimulation) and indicates times of maximal response. A global assessment of the amount of all voltage differ-

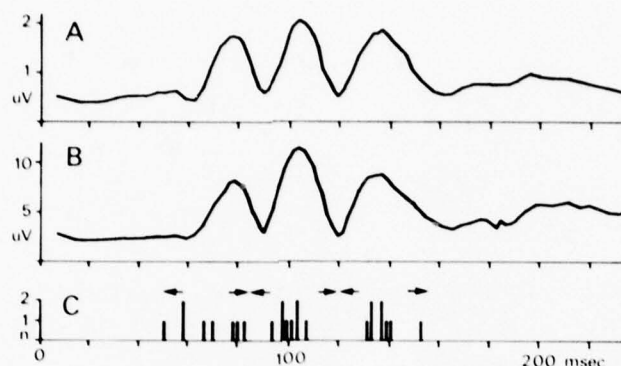


Fig. 3. A: Amount of relief of the evoked field distribution as a function of time ("hilliness curve"); B: Maximal voltage difference between any two electrodes within the field as a function of time. A and B during upper hemiretina stimulation, same data as Figs. 1A and 2. C: Times of peaks of hilliness curves obtained from eight subjects during upper hemiretina stimulation. Peaks determined for three analysis periods (arrowheads). (From Lehmann and Skrandies, in prep.)

ences between all electrodes in the scalp field is the computation of the average, absolute deviation of voltage per electrode from the mean of all instantaneous voltages (average reference). This mean of the absolute voltage deviation per electrode is a measure of the amount of relief or "hilliness" of the scalp field. The hilliness (Lehmann 1971) is a measure of the relative power of the evoked field distribution. The values can be plotted against time (Fig. 3A), and typically the resulting curve for a given subject is similar, although not identical, to the curve of the maximal voltage differences between any two electrodes in the field, as Fig. 3A shows. Both curves show three distinct peaks as 77, 102 and 135 msec. We now may go back to Fig. 2 and examine the scalp field distributions which exist at about the occurrence time of the peak values of the hilliness curve. We note that the distributions at 100 and 130 msec are quite distinct and show occipital maximal values of inverted polarity at the two times. These occipital extreme values are, of course, also seen in conventional waveshape recordings.

We collected scalp field data from eight subjects using upper hemiretina checkerboard stimulation (15-26 deg. arc field). The hilliness curves were constructed for each subject and searched for peak values during the three peak periods of 50-85 msec, 85-120

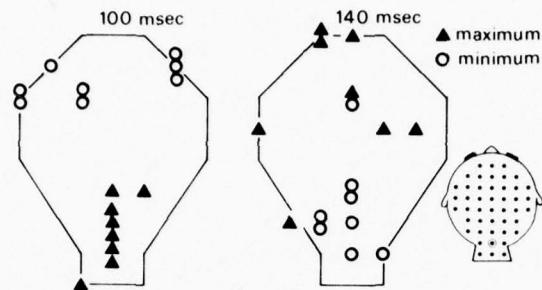


Fig. 4. Scalp electrode locations of maximal (triangles) and minimal (circles) field values at two peak times (about 100 and 140 msec) of the individual hilliness curves (see Fig. 3C) of eight subjects. Upper hemiretina stimuli. Head with electrode array seen from above; outline of plots indicates array. (From Lehmann and Skrandies, in prep.)

msec and 120-155 msec latency. The resulting distribution of peak times is illustrated in Fig. 3C. There is considerable scatter for the peaks during the earliest analysis period, but the two later hilliness peaks show a satisfying consistency of latencies across subjects. Thus these two moments in time after the stimulus may be used as times of maximal response for the subject population. In order to determine the spatial distribution of the peaks we now plot the scalp locations of the maximal and minimal field values at the subjects' individual peak latencies of their hilliness curves (Fig. 4). It is evident that the group data show an occipital positivity at about 100 msec and an occipital negativity at about 140 msec. Thus this method determines objectively time and scalp location of the major components of the brain response to checkerboard reversal stimuli.

Right Versus Left Hemiretina

Several papers investigated the shapes of potentials evoked by right or left half field stimulation (Cobb and Morton, 1970; Lesevre, 1972; Barrett et al., 1976; Blumhardt et al., 1977). The results were contradictory as to correct lateralization of the evoked responses on the scalp. We suggested (Europ. EEG Meeting, Venice, 1976) that the degree of "wrong" lateralization may increase with target size. If we inspect a subject's scalp fields which were evoked by hemiretinal stimulation (Fig. 5), things turn out to be somewhat more complicated (the fields of Fig. 5 were con-

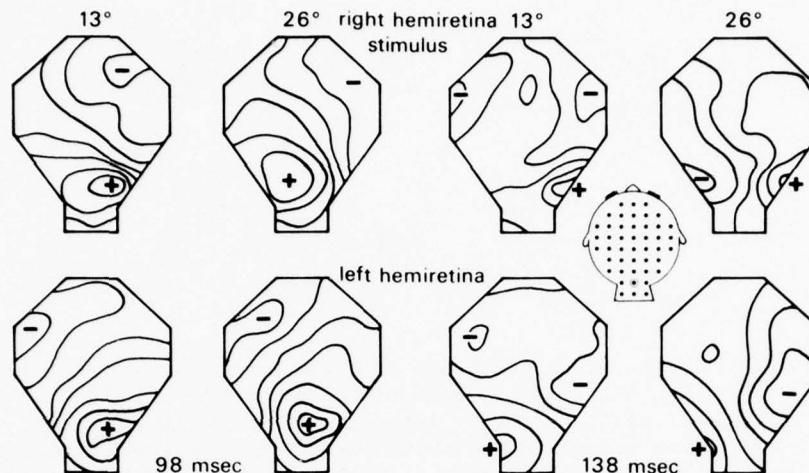


Fig. 5. Scalp field distributions (equipotential-line maps) for right and left hemiretina stimulation at the peak times of the subject's hilliness curve. Each equipotential line = voltage step of 1 μ V. (+) and (-) indicate extrema areas, not exact electrode locations.

structured at times of maximal hilliness of the evoked potential field; these times were identical for upper, right and left hemiretinal stimulation). We note that for small target size, the field at 98 msec is lateralized over the right occiput for both right and left hemiretina stimuli. However, the positive portion of the field which was evoked by right hemiretinal stimuli has a steeper gradient to the right side, whereas that for left hemiretina stimuli is steeper to the left side. In other words, for these small targets there is at 98 msec a lateralization of the occipital field distribution towards the "correct" side, ipsilateral to the stimulated hemiretina. At the same latency for 26 deg. arc targets, the opposite shift of the occipitally evoked, positive portion of the field towards the "wrong" side, contralateral to the stimulated hemiretina, is seen in Fig. 5. The fields at 138 msec appear to be largely similar for small and large targets with the maximum over the "correct" side in the occipital area and the minimum more anterior over the "wrong" side.

The relative shift of location can be expressed as a vector whose origin is, say, at the electrode that detects the maximal field value for right hemiretinal stimuli and whose head is at the electrode which detects the maximal field value for left hemiretina

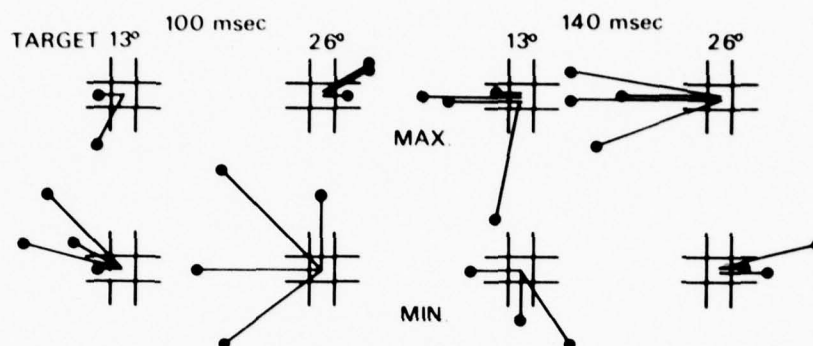


Fig. 6. Vectors indicating direction and amount of change of location of the evoked maximal (MAX) and minimal (MIN) field values of four subjects with change of the stimulation from right to left hemiretina, for the two target sizes and for the two hilliness peak times. Center of reference grid is the location of maximal (minimal) value for right hemiretina stimuli; dots give relative location of the same value for left hemiretinal stimuli; dots give relative location of the same value for left hemiretinal stimuli in the different subjects; no dot = case of no change; one square = one interelectrode distance. Head seen from above, nose up. Two of the subjects showed no change for maximal value location with 13° targets at 100 msec, but there was a change of the field distribution in the same direction as in the other two subjects (see Fig. 5 for example).

stimuli. We examined four subjects (including the subject of Fig. 5) with 13 and 26 deg. arc checkerboard stimuli using lateralized retinal stimulation. We plotted the shifts of the maximal and minimal field values at the respective peak times of the subjects' hilliness curves. Fig. 6 shows that at 100 msec the maximal field values shift towards the "correct" side for 13 deg. arc targets (two of four subjects) and to the "wrong" side for 26 deg. arc targets (three of four subjects); cases without shift of the maximal values showed displacements of the field distributions similar to the other subjects (Fig. 5 shows an example). The minimal field values at 100 msec (i.e., the anterior field troughs) shift towards the "correct" side for both small and large targets. The later (140 msec) components show clear results for the maximal field value but less consistent results for the negative extreme value. Fig. 5 illustrates this observation inasmuch as the maximal field value is centered occipitally over the "correct" hemisphere, whereas the minimal value typically is more anterior over the "wrong" hemisphere. The occipital response at 140 msec is expected to be

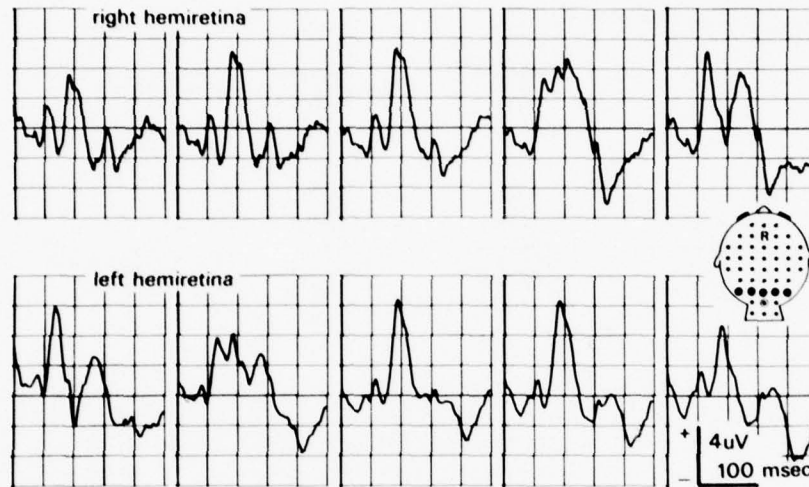


Fig. 7. Evoked potential waveshapes reconstructed from multichannel data of one subject, for right (upper row) and left (lower row) hemiretina stimulation (26° target), between an anterior midline electrode (R) and a left to right transverse row of five electrodes 3.5 cm above theinion (heavy dots in inset). Note the positive component at 100 msec over the "correct" hemisphere. Same data as in Fig. 5.

negative, as was demonstrated with centered retinal stimulation (Figs. 2 and 4). With lateralized retinal stimuli we observe that this minimum appears over the "wrong" hemisphere in line with the "wrong" localization of the positive extreme value at 100 msec. But at 140 msec the occipitally dominating field characteristic which is evoked by lateralized stimuli is the positive extreme value over the "correct" hemisphere. This result is easily picked up and quite impressive in conventional waveshape recordings against an anterior reference (Fig. 7; see also Fig. 1 in Blumhardt et al., 1977) which show a late positive response over the "correct" occiput.

One may argue that since the response to small targets probably is generated by the foveal projection area around the occipital pole of the hemisphere, the maximal field value tends towards the "correct" side. On the other hand, since peripheral retinal areas are projected to cortical regions on the medial brain surface, the maximal scalp field value then tends to appear over the "wrong"

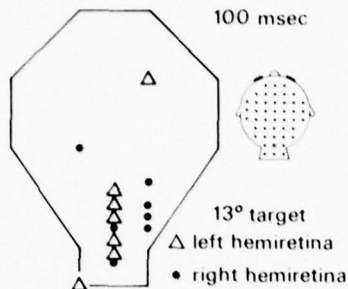


Fig. 8. Absolute scalp locations of positive extreme field values at peak times of individual hilliness curves (seven subjects) at about 100 msec for right and left hemiretina stimulation with 13° target. (From Lehmann and Skrandies, in prep.)

side (see also Barrett et al., 1976) for larger targets.

The observation that the response at 100 msec shows an occipital maximum for lateralized stimuli, as well as for centered stimuli, whereas the 140 msec response shows an occipital maximum for lateralized stimuli but an occipital minimum for centered stimuli, is indicative of activity of two different neural generator populations.

The described group characteristics of relative location change of extreme field values do not imply consistency of the absolute locations across subjects. Fig. 8 demonstrates the absolute scalp locations at individual hilliness peak times around 100 msec for seven subjects using left and right hemiretinal, 13 deg. arc targets. Obviously there is a considerable scatter of the absolute locations between subjects, although the population shows the general tendency for field shifts towards the "correct" hemisphere when the stimulation is changed from one to the other retinal half.

Upper Versus Lower Hemiretina

When the upper hemiretina is stimulated selectively, field distributions are observed with maximal values at a more anterior location than when the lower hemiretina is stimulated (Lesevre, 1973). Fig. 9 illustrates such scalp field series (15 deg. arc targets). These scalp fields reach maximal values at an earlier time for upper than for lower hemiretinal stimuli. These latency differences might be critical when potentials evoked by checkerboard reversal are used for clinical MS diagnosis (Halliday et al., 1973).

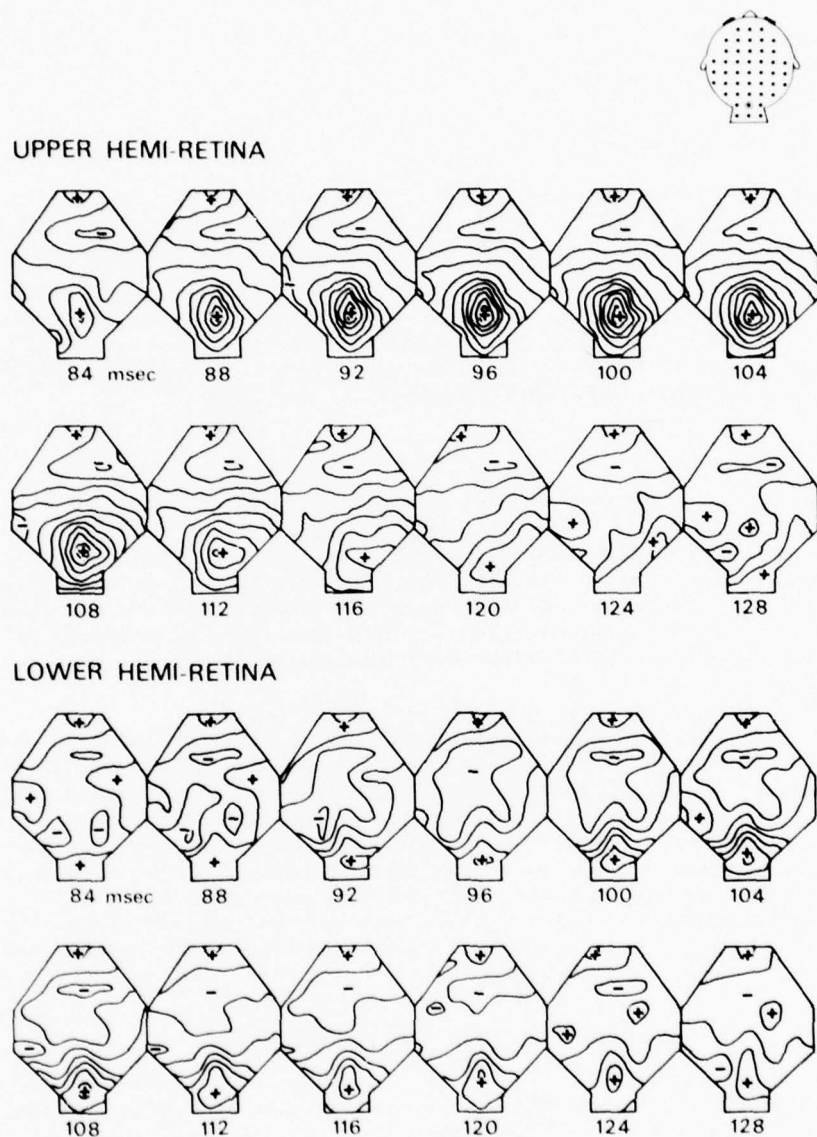


Fig. 9. Equipotential-line maps of average scalp field distributions evoked by stimulation of the upper and lower hemiretina (15° field, 50° checks). Head seen from above, nose up. Each equipotential-line represents a step of $2.2 \mu\text{V}$. (From Lehmann and Skrandies, in prep.)

In an earlier paper on this problem (Lehmann et al., 1977) we had shown that scalp field latency differences may look like waveform inversions in conventional recordings. We had demonstrated scalp fields evoked by lower hemiretina stimuli where the occipital field peak was at the border of the recorded area, and accordingly field peak migration towards the recording area was not excluded as a possible cause of the latency differences.

To settle the latency question we will have to use subjects whose field peaks remain in the recorded area during the crucial time. Since the scalp fields are centered at the occiput around the sagittal midline and since the anterior distribution is flat in these stimulus conditions, we need only to search a midline row of electrodes in order to (a) construct a curve of potential differences over time between any two of the eight midline electrodes and (b) make certain that the maximal values are neighbored by non-extreme field values so as to rule out peak migration. Out of twenty-five subjects, only five fulfilled this latter restriction. Profiles of the instantaneous voltages at the eight electrodes along the midline were constructed and searched for maximal potential differences at each analysis time (plotted vertically in the example of Fig. 10). The time of the largest value of the voltage differences between any two electrodes determined the response latency. Median latencies of the five subjects for upper and lower hemiretina stimuli are given in Table I; the difference is significant at $p < .031$ in Walsh Tests.

These latency differences between upper and lower hemiretina evoked potentials are in line with a number of anatomical (e.g., Osterberg, 1935) and behavioral observations in man, amongst them reports on a longer reaction time for lower hemiretinal stimuli (e.g., Payne, 1967).

Table I. Median response latencies of five subjects, in msec, at 1.6 checkerboard reversals/sec (15° , $40'$).

Stimulated hemiretina		upper	lower
subject	1	98.0	110.0
"	2	96.5	116.0
"	3	99.0	116.0
"	4	94.0	106.0
"	5	104.0	115.0

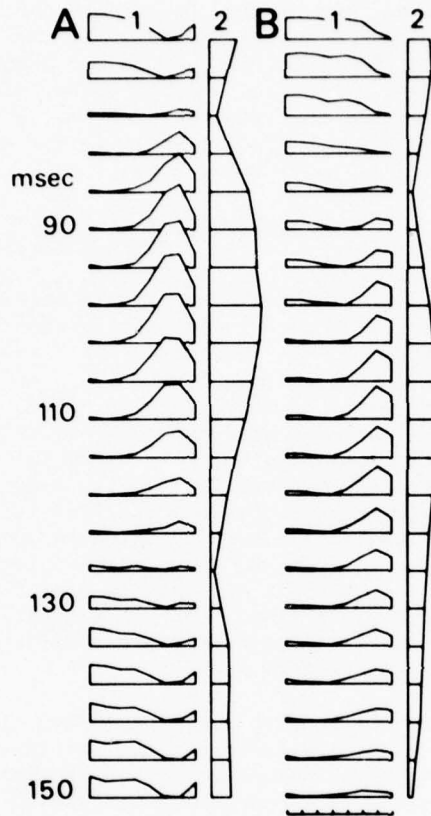


Fig. 10. Profiles of average evoked potential fields (column 1) from an anterior to posterior midline row of eight electrodes (left to right, horizontal bar with marks at bottom). A upper, B lower hemiretinal stimuli. The lowest voltage determines baseline of each profile. The maximal voltage difference between any two electrodes in a given profile is shown by a horizontal bar in column 2. (From Lehmann and Skrandies, in prep.)

SUMMARY

Using multichannel recordings, the latencies of components of potentials evoked by checkerboard reversal were defined by (a) the maximal voltage difference between any two electrodes in the field or by the more general term (b), the maximal value of the mean voltage deviation per electrode from the mean voltage of all electrodes

(hilliness, or relative power). Scalp location of the components was defined as point of maximal (or minimal) voltage on the scalp. Two response times were found in the subject population: 100 and 140 msec. For centered stimuli, there was an occipital maximum at 100 msec and an occipital minimum at 140 msec. With lateralized hemiretinal stimuli, the lateralization of the evoked fields depended on target size: at 100 msec, 13 deg. arc targets evoked maxima which tended towards the "correct" side ipsilateral to the stimulated hemiretina, whereas with 26 deg. arc targets, maxima were found over the "wrong" side. The 140 msec response for lateralized stimuli was occipitally positive (as opposed to negative for central fixation) and lateralized over the "correct" side for small and large targets. The occipital polarity for the late response changes to lateralized in comparison to centered stimuli. This is not true for earlier responses and indicates two different neural generators. Upper hemiretina stimuli produced shorter (mdn:12 msec) response latencies than lower hemiretina stimuli. Scalp field migration was excluded as possible cause of this difference. Several behavioral and anatomical observations are in agreement with this difference. For clinical applications it appears advisable to test hemisphere functions with larger size stimuli and to consider the latency differences between upper and lower hemiretinae.

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SPONTANEOUS AND EVOKED CEREBRAL ELECTRICAL ACTIVITY AND LOCALIZATION
OF LANGUAGE FUNCTION IN CHILDREN WITH MINIMAL CEREBRAL DYSFUNCTION

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INTRODUCTION

One of the major theoretical constructs in the field of cognitive science holds that higher order cerebral tasks are performed in so-called association areas of the cortex, or at least in brain regions different from those serving primary sensorimotor functions. An important element in this concept is that these higher order tasks may also be performed differentially and preferentially by the left and right hemispheres. Most of the evidence for such localization of function has been indirect, derived from clinical-behavioral observations and either post-mortem or ante-mortem diagnostic procedures demonstrating alterations in brain structure.

Neuropsychological experiments (Kimura, 1961; Dimond and Beaumont, 1974; Gazzaniga, 1974; Milner, 1974), cerebral bloodflow studies (Ingvar, 1974) and recording and analysis of brain electrical activity (Harnad et al., 1977; Desmedt, 1977) have all been used in attempts to obtain direct evidence of higher order processing and the distribution or location of such activity within and between the hemispheres in the intact brain. The rationale for such investigations is not only to seek evidence of normal brain mechanisms subserving cognition, language, etc., but also to respond to the powerful motivation of clinical need. At present clinical problems involving higher order dysfunction are extremely difficult to evaluate in objective, quantifiable terms.

Neuropsychological experiments with split brain patients and employing hemisphere directed stimuli have provided unequivocal evidence of differential activity of the left and right hemispheres,

but the applicability of these findings to the intact, integrating brain is uncertain. Cerebral bloodflow recording has also provided direct and definite evidence not only for lateralization of function but for intrahemispheric localization of function as well. However, such experimental procedures are extremely specialized and expensive. They can be accomplished only in very few centers, and the necessity for injection of a radioisotope would limit the ethical application of such studies to cases with real medical need.

Electrophysiological studies of cognitive and conative function have been broadly used, and it is generally accepted that high level processing of sensory input and the cerebral activity involved in preparing for and carrying out action will influence brain electrical patterns. Beyond this point there is very little agreement. The hypothesis that the brain events critical for the appropriate processing of sensory input, formation of percepts and concepts, memory retrieval, association, evaluation, volition and action will be signalled by specific and identifiable changes in the electrical patterns recordable from the scalp is intuitively appealing. But while the literature abounds with reports of changes in or the appearance of brain waves which are supposedly correlates of some specific higher order process, for virtually none of these is there general agreement both about the true cerebral origin of the activity recorded and the specific brain process giving rise to the activity. The relevant literature has recently been extensively and critically reviewed (Donchin et al., 1977; Donald, 1978) and will not be reported here. But with the possible exception of the early segment of the Bereitschaftspotential (BSP) or motor potential complex, it is clear that there is as yet no universally accepted electrophysiological evidence of localization (or, for that matter, lateralization) of higher cerebral function that even approaches in precision the details of the constructs derived from clinical studies.

Our own experience in this area began with a search for a motor speech analog of the contingent negative variation (CNV or slow component of the BSP; some investigators consider them to be equivalent), the results of which have been published elsewhere (Low et al., 1973; Low et al., 1976; Low and Fox, 1977). The motivation was primarily clinical need. We are frequently required to assess patients for possible brain surgery, and for whom an unequivocal determination of hemisphere dominance for language is essential. The carotid Amytal test of language dominance is considered reliable, but it is not without risk and cannot be used at all in young children. A noninvasive substitute, applicable to children, would be very valuable.

Our data, now from more than 125 recording sessions with normal subjects and patients, led us to conclude that there is a slow potential recordable from the posterior and inferior frontal regions

prior to speech in a manner analogous to the vertex CNV in the usual cued reaction time paradigm, and that these speech CNVs do show asymmetries which in grouped data can be related to cerebral dominance for language. However, the procedures involved present serious methodological difficulties as several investigators, including ourselves, have documented (Szirtes and Vaughan, 1977; Grozinger et al., 1977; Low and Fox, 1977). Furthermore, we were unable to achieve better than 80% accuracy in prediction of hemisphere dominance (as finally determined by the carotid Amytal test) when using speech CNV criteria alone.

Because a number of reports in the literature have suggested that other measures of cerebral electrical activity are related to language dominance (Cornil and Gastaut, 1947; Galin and Ornstein, 1972; Callaway and Harris, 1974; Butler and Glass, 1974; Beck et al., 1975; Donchin et al., 1977), we reasoned that some of these could be used either to strengthen the evidence of lateralization in the presence of a consistently asymmetrical CNV or to provide definitive lateralizing information when the CNV asymmetry was variable or inconsistent (as is often the case).

Consequently, we developed a comprehensive test "battery" including a number of neurophysiological measures (i.e., visual evoked potentials to words and pattern reversal, the CNV, EEG power and coherence spectra) which we anticipated would assist both in the assessment of hemisphere dominance and the demonstration of regional changes in brain electrical activity during reading, speech and other activities presumed to engage primarily the left or the right hemisphere. We have applied our neurophysiological test battery in recordings from fifty-one children who are participants in a study being conducted by the U.B.C. Division of Pediatric Neurology. The study is a prospective one of children born prematurely and/or with low birth weight compared to a group of age-matched full birth weight children. We have, therefore, had access to a very highly selected group of subjects with very detailed gestation, birth, neurological, neurophysiological and developmental histories, all of whom have been followed clinically for up to 15 years.

Data analysis was intended to provide answers to primarily two questions: (1) Are there consistent relationships between the different electrophysiological measures, functional laterality and hemisphere dominance for language so that one may be reliably predicted from another in a given individual? (2) Are there consistent electrophysiological correlates of minimal cerebral dysfunction?

METHOD

Subjects for the study were all children between the ages of 12-1/2 and 15 years. They included twenty-nine normal controls

(seventeen male and twelve female) and sixteen with the MCD syndrome (eleven male and five female). All were proven dextrals by laterality testing (handedness, footedness, eyedness). Data from an additional six sinistrals (four MCD and two normal) are not included in this report.

To obtain the diagnostic criteria for the MCD syndrome, clinical assessments were made in four major areas, i.e., neurological signs, organic behavioral syndrome signs, routine electroencephalogram findings (including hyperventilation, photic stimulation and sleep) and psychometric testing (Table I). Subjects were given a score of 0 for normal, 1 for abnormal or 1/2 for borderline in each area. The original clinical diagnostic classification was based upon the

TABLE I
DIAGNOSTIC CRITERIA - MCD

I. Organic Behavior Syndrome

Excessive motor activity, impulsiveness, destructiveness, short attention span, distractibility, irritability, mood swings, perseveration, unpredictability, sleep disturbance.

II. Neurological Abnormalities

Eye - Squint, nystagmus, etc.

Motor - Dystonia, abnormal reflexes, involuntary movements, poor gross or fine coordination, cross-laterality.

Sensory - Finger agnosia, astereognosis, lack of R-L distinction

Congenital Stigmata - Hypertelorism, abnormal palm prints, multiple cafe au lait spots.

III. Psychometric Abnormalities

WISC - Full scale IQ assumed 80 +

- Significant (15+) difference verbal/performance

- Subtest scatter

Good Enough - Harris man/woman average IQ

Knox Cube

Vocal Encoding

IV. EEG Abnormalities

Routine 16-channel recording; awake, asleep, hyperventilation and photic stimulation.

total of the four scores with 0 - 1.5 considered normal and 2 - 4 considered MCD.

All electrophysiological recordings were done in an electrically shielded, sound-deadened room with the subjects seated in a reclining chair. Word stimuli were displayed via a 24 cm monochrome TV monitor placed 1 meter in front of the subject's face. The center of the screen was marked for visual fixation. The stimulator for pattern reversal VEPs was a grid of red light-emitting diodes.

Recordings were done with a Beckman Type "R" Dynograph. The recording system bandwidth was 0.025 Hz to 100 Hz (3 dB points) and preamplified EEG signals were led directly to the A/D converters of a PDP 11/20 computer which controlled all of the stimulus presentation and data acquisition. During all recording sessions an automatic artifact rejection routine was used which excluded a trial from the average if the voltage in the electro-oculogram (EOG) channel exceeded a preset limit empirically determined at the beginning of the session (Low, 1977).

The neurophysiological test battery included:

(a) Power spectral analysis. This was obtained for four electrode positions (F3, F4, P3, P4 - paired ear reference) during four conditions - resting with eyes open, resting with eyes closed, performance of a right hemisphere dependent task (Street Gestalt completion) and performance of a left hemisphere dependent task (WAIS Similarities Subtest for Children). For each condition the power in the four canonical EEG frequency bands was measured during ten 4 sec sampling periods.

(b) Coherence functions. Coherence in the alpha band was calculated for F3/F4, P3/P4, F3/P3, F4/P4 during the above four conditions.

(c) Speech CNVs. The speech CNV was recorded from eight temporal and posterior frontal scalp locations as illustrated in Fig. 1 using the contralateral ear as reference. The computer controlled paradigm presented a 3-5 letter word as S1 on the video screen. The word was displayed for 50 msec, and 1.5 sec later a tone pip occurred as S2. Subjects were instructed to watch the center of the screen, read the word as it appeared and to say the word aloud as soon as the tone sounded. Up to thirty different words were presented, and averages of blocks of fifteen or thirty trials were obtained in 2.3 sec epochs each beginning 0.5 sec prior to the appearance of the word on the screen.

CNV measures were derived as integrations over time of the negative and positive voltage in each of the two successive 500 msec intervals preceding the onset of S2 as illustrated in Fig. 2. The

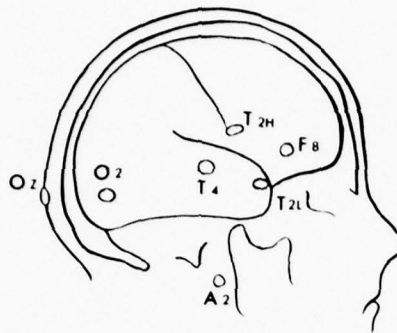


Fig. 1. Electrode placements for recording speech CNVs, WEPs and pattern reversal VEPs. TH and TL are 2 cm above and 2 cm below a point midway between the midtemporal (T3,T4) and posterior-frontal (F7,F8) electrodes.

data from the second interval was later excluded from the analysis because of possible artifact contamination.

(d) Visual evoked potentials to words (WEPs). From the same eight scalp locations, four amplitude measurements of the WEP to the word presented as S1 in the CNV paradigm were made as shown in Fig. 2, i.e., a-b, b-c, c-d, d-e.

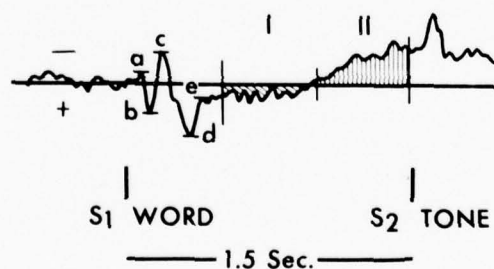


Fig. 2. Illustration of the WEP peak-to-peak amplitude measurements (a-b, b-c, c-d, d-e) and speech CNV voltage integrations (a positive and a negative value are possible in each time segment I and II).

(e) Pattern visual evoked potentials. Using the reversing red light pattern stimulator, VEPs were recorded from three electrode locations (O1, O2 and O2 - paired ear reference). Stimuli were delivered to the left and right eyes independently, and responses were recorded and averaged in blocks of 100.

Measures of patterned visual evoked potential parameters were derived as the latencies of P100 and N200 components at the O2 electrode position with left and right eye stimulation and the amplitude (peak-to-peak) of the P100 - N200 segment at the O1 and O2 electrode positions with left and right stimulation.

Due to the length of time required to accomplish all of the above and to avoid subject fatigue the procedures were divided into two parts, and the subjects completed the two recording sessions on different days separated by as much as several weeks. Specific test items included in a given day's recording were variable, but usually the power spectra, coherence functions, speech CNVs and evoked potentials to words were obtained during a single session.

RESULTS

From the 156 separate neurophysiological-dichotic listening measures we have derived an additional 300 variables including inter- and intrahemispheric ratios of the measures listed above. This extremely large data base presents many analytical possibilities, and while a number are being pursued, this report is only concerned with the question of correlations between electrophysiological measures of differences between left and right hemisphere activity (termed interhemispheric ratio variables) and with the differences between all of the measures in the normal and MCD subject groups.

Covariance in Electrophysiological Measures

The neurophysiological data from the twenty-nine normal subjects (all dextrals) were taken separately and analyzed for possible covariances between interhemispheric measures made of speech CNV, evoked potential and EEG power spectra at rest and during differential task engagement. A complete search for the dependencies between these variables was impossible because of the relatively small number of subjects.

As an initial step a correlation matrix was calculated for all of the interhemispheric (left-right) ratio variables. This showed no significant correlations. Principal components (Bio-Med "P" series, program P4R; Dixon, 1977) were then calculated for each of the three sets of variables, i.e., CNVs, VEPs and EEG excluding

only the intrahemispheric ratio variables. The first principal component of the CNV data measured left-right differences in a way analogous to the second principal component of the whole data set (see below, Table IV). The other two data sets did not yield similar left-right principal components. The CNV first principal component was then used as the dependent variables in separate stepwise regression calculations (Bio-Med "P" series, program P2R) with each of the two other data sets' (word evoked potential and EEG) principal components as independent variables. Two further stepwise regression runs were made, again with the CNV first principal component as the dependent variable and each of the two other data sets' untransformed variables as independent variables. Although a few of the resulting correlations might have been considered significant, no interpretable or consistent pattern emerged, and it was concluded that these scattered correlations arose by chance.

Between Groups Differences in Electrophysiological Measures

In considering the possible separation of the normal and MCD subject groups a preliminary analysis of the effect of combining the four separate diagnostic scores (neurological exam, O.B.S., psychological testing and routine EEG findings) into a single score was undertaken. It was found that the psychological and EEG scores were less reliably related to the other two (see Table II which shows the correlation the correlation matrix of all four scores) and had higher variances. Consequently it was decided to use as a final diagnostic score a weighted sum of the four subscores with the EEG and psychological testing carrying one-half the weight of

TABLE II

CORRELATION ANALYSIS OF FOUR DIAGNOSTIC VARIABLES

	NEURO	OBS	EEG	PSYCH	MEAN	ST.DEV.	R ² *
NEURO	1.000				0.3222	0.356	0.384
OBS	0.568	1.000			0.278	0.362	0.351
EEG	0.328	0.187	1.000		0.300	0.418	0.108
PSYCH	0.287	0.325	0.075	1.000	0.400	0.434	0.121

* Squared multiple correlation of each variable with the other three.

the other two. This resulted in a better regression (more significant) analysis of the CNV variables against diagnostic score.

Since the diagnostic score did not have an obvious bimodal distribution, for further analysis the data were treated in a single group, and multivariate regression analysis with the diagnostic score as the dependent variable was undertaken. The speech CNV measurements yielded forty-eight variables grouped into three categories: a) integrated amplitude of speech CNV, b) interhemispheric ratios of these integrated amplitudes and c) intrahemispheric ratios of the integrated amplitudes. Since there were forty-eight variables and only forty-four subjects, considerable data reduction was necessary, and two methods were used. (One further subject was eliminated. The regression analysis indicated that this subject was an outlier, and this clinical diagnosis carried a special note indicating possible serious neurological problems.) The first was stepwise multivariate linear regression (from UCLA Bio-Med "p" series, program P2R) used to select from the forty-eight variables the subset best related to the MCD diagnostic score. The initial (step 0) partial correlations are listed in Table III. The criterion chosen for entering variables was to maximize the change in the residuals (called F method by P2R).

An intrahemispheric ratio ($F8/F8+T4$, speech CNV, early segment negative integration) was entered first. Examination of Table III shows that the category of right intrahemispheric ratios contains much information related to MCD, with temporal interhemispheric ratios and temporal right hemispheric positive integrations nearly as significant. The F-to-enter values for the second step of the stepwise regression program show that most of the negative integration variables were sufficiently correlated with the chosen variable that their F-to-enter values dropped. Many of the positive integration values, however, had increased F-to-enter values for the second step, and the entry of the T4 positive integration variable increased the significance of the regression over that of the first step. The F ratio at this point was highly significant [$F(2,41)=24.77, p$]. The variables entered in the next several steps decreased the significance of the F ratio.

A closer examination of the data for the intrahemispheric ratios indicated that minimal cerebral dysfunction is indicated by large ratios while normal ratios are more likely to be near 0.5 (the ratio $F8/F8+T4$ equals 0.5 if F8 equals T4). In the case of $F8/F8+T4$, one half of the subjects with the original diagnosis of normal had ratios below 0.5 and one-half above (Fig. 3). Thirteen of the fifteen subjects diagnosed as having MCD had ratios above 0.5. In fact eleven of the fifteen had ratios above 0.7.

The second method of data reduction was to calculate the principal components of the standardized CNV variable data matrix (using

TABLE III

CORRELATIONS OF THE SPEECH CNV VARIABLES WITH THE DIAGNOSTIC
VARIABLE DETERMINED BY STEPWISE REGRESSION ANALYSIS

Left Hemisphere Measurements			Left Intrahemispheric Ratios		
	Negative Integrations	Positive Integrations		Negative Integrations	Positive Integrations
F7	0.348	-0.278	F7/F7+T1H	0.005	-0.157
T1H	0.226	-0.064	F7/F7+T1L	0.283	0.008
T1L	0.290	0.019	F7/F7+T3	0.397	-0.092
T3	0.074	0.117	T1H/T1H+T1L	0.011	0.202
			T1H/T1H+T3	0.284	0.022
			T1L/T1L+T3	0.325	-0.134
Interhemispheric Ratios					
	Negative Integrations	Positive Integrations	Right Intrahemispheric Ratios		
				Negative Integrations	Positive Integrations
F8/F8+F7	0.371	-0.126	F8/F8+T2H	0.342	-0.201
T2H/T2H+T1H	0.351	-0.255	F8/F8+T2L	0.448	-0.393
T2L/T2L+T1L	0.491	-0.474	F8/F8+T4	0.584	-0.372
T4/T3+T4	0.559	-0.366	T2H/T2H+T2L	0.197	-0.239
			T2H/T2H+T3	0.411	-0.329
			T2L/T2L+T4	0.361	-0.099
Right Hemisphere Measurements					
	Negative Integrations	Positive Integrations			
F8	-0.003	0.026			
T2H	-0.169	0.177			
T2L	-0.325	0.454			
T4	-0.418	0.504			

Bio-Med, program P2R). The second principal component was the most highly correlated {correlation = 0.58552, F ratio for the regression 21.91 [F(1,42)]} with the diagnostic score and was comparable to F8/F8+T4 in this respect. No other principal component in combination with the second supplied sufficiently different information to increase the significance of the F ratio.

The second principal component (Table IV) can be interpreted as indicating a difference between the left and right hemispheric

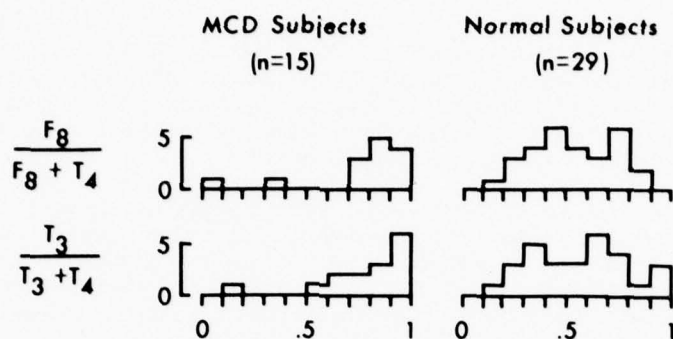


Fig. 3. Histogram of the distribution of the early segment speech CNV ratio values (intra- and interhemispheric) in normal and MCD children.

TABLE IV

SECOND PRINCIPAL COMPONENT OF SPEECH CNV DATA

This table lists the second eigenvector values for the 24 positive integration variables of the speech CNV data. The eigenvector values for the 24 negative integration variables are not included because they provided essentially the same information.

Left Hemisphere Measurements		Interhemispheric Ratios		Right Hemisphere Measurements	
F7	-0.12*	F8/F8+F7	-0.23**	F8	0.13*
T1H	-0.09	T2H/T2H+T1H	-0.24**	T2H	0.17*
T1L	-0.14*	T2L/T2L+T1L	-0.28**	T2L	0.24**
T3	-0.07	T4/T4+T3	-0.29**	T4	0.25**
Left Intrahemispheric Ratios				Right Intrahemispheric Ratios	
F7/F7+T1H	-0.06			F8/F8+T2H	-0.13*
F7/F7+T1L	-0.04			F8/F8+T2L	-0.18*
F7/F7+T3	-0.07			F8/F8+T4	-0.17
T1H/T1H+T1L	0.02			T2H/T2H+T2L	-0.09
T1H/T1H+T3	-0.04			T2H/T2H+T4	-0.09
T1L/T1L+T3	-0.07			T2L/T2L+T4	-0.04

* Emphasis of values greater than 0.10

** Emphasis of values greater than 0.20

CNV measures. The largest contributions to the principal component are almost exclusively from the left-right interhemispheric ratios, and the left hemisphere negative integrations are negatively weighted while the right hemisphere negative integrations are positively weighted. It should be noted that the intrahemispheric ratios contribute little to this principal component.

Examination of Table IV shows that relatively larger left hemisphere negative integration measures result in a smaller (more negative) principal component value. Since the principal component is negatively correlated with the MCD diagnostic variable, relatively larger left hemisphere integrations are positively associated with MCD.

The interhemispheric ratio with the highest principal component coefficient was $T3/T3+T4$. For this variable (Fig. 3B) fourteen normals had values below 0.5, and sixteen above, while fourteen of the fifteen MCDs had ratios above 0.5 (eleven above 0.7).

The word evoked potential variable most significantly related to the MCD diagnostic variable, according to stepwise regression, was an intrahemispheric ratio ($F8/F8+T4$) for the N100 peak [$p = 0.41$, $F(1,42) = 8.59$]. The second most significant was an intrahemispheric ratio ($T2L/T2L+T4$) for P300 [$p = 0.40$, $F(1,42) = 7.77$]. All other groups of variables were clearly less related. For the N100 variable eighteen of twenty-nine normals had values above 0.5, but only six of these were above 0.6 while eleven of fifteen MCDs had values above 0.6. For P300 thirteen of sixteen normals had ratio values above 0.5, with six having values above 0.6, while ten of fifteen MCDs had values above 0.6. Some components of the word evoked potential, like the early segment speech CNV, were therefore more asymmetrical (or less evenly distributed within one hemisphere) in MCD children than in normals.

Principal components were calculated separately for the variables derived from each of the four evoked potential peak measurements. The third principal component for the N100 variables was significantly related to the MCD diagnostic variable [$p = -0.464$, $F(1,42) = 11.53$]. The N100 principal component coefficients are presented in Table V. The right intrahemispheric ratios contribute most heavily to this principal component and, consistent with the speech CNV data, a negative principle component score (higher intrahemispheric ratios) indicates minimal cerebral dysfunction.

In a similar fashion, multivariate linear regression and stepwise regression were utilized in analysis of the ten pattern visual evoked potential variables. This analysis demonstrated that the children with the highest degree of minimal cerebral dysfunction tended to have the lowest amplitude visual evoked potentials at O1, the shortest N160 latencies and highest pattern evoked potential amplitude at O2.

TABLE V

PRINCIPAL COMPONENT OF WORD EVOKED POTENTIAL PEAK N100
Numbers are the eigenvalues of the variables listed

Left Hemisphere Measurements		Interhemispheric Ratios		Right Hemisphere Measurements	
F7	-0.07	F7/F7+F8	0.04	F8	-0.10
T1H	0.06	T1H/T1H+T2H	0.06	T2H	0.05
T1L	0.01	T1L/T1L+T2L	-0.09	T2L	0.09
T3	0.13	T3/T3+T4	-0.14	T4	0.33

Left Intrahemispheric Ratios		Right Intrahemispheric Ratios	
F7/F7+T1H	-0.22	F8/F8+T2H	-0.26
F7/F7+T1L	-0.09	F8/F8+T2L	-0.30
F7/F7+T3	-0.27	F8/F8+T4	-0.45
T1H/T1H+T1L	0.12	T2H/T2H+T2L	-0.10
T1H/T1H+T3	-0.06	T2H/T2H+T4	-0.36
T1L/T1L+T3	-0.20	T2L/T2L+T4	-0.35

The EEG variable first chosen by the stepwise regression procedure was intensity in the Delta (0-4 Hz) frequency band from electrode placement F3, eyes open condition [$p = 0.32$, $F(1,42) = 4.81$]. In general minimal cerebral dysfunction was positively related to delta and theta intensity and negatively related to alpha intensity. The second best variable [$p = 0.32$, $F(1,42) = 4.81$] was an intrahemispheric ratio, $F3/F3+P3$, of average intensities in the alpha band for the similarities condition. The frontal interhemispheric ratios and left hemisphere intrahemispheric ratios for each condition were nearly as significant. The variation in these variables was too great, however, to ascertain their distribution with respect to the symmetric ratio value of 0.5.

None of the EEG principal components was significantly related to the MCD diagnostic variable.

DISCUSSION

There are two main conclusions which follow from these experiments. The first is that we have failed to demonstrate a consistent correlation between electrophysiological measures presumed to reflect or to be affected by different activity in the two hemispheres

related to hemisphere dominance (at least as far as such dominance is indicated by functional laterality). This is disappointing in that we hoped to be able to show that combinations of such measures would provide strong corroborative evidence of language dominance in clinical situations.

One important reason for the lack of statistically significant correlations among our event related and ongoing EEG potential measures is their marked variability within and between subjects. There were left-right hemisphere differences in several measures both at rest and during specific tasks presumed to depend primarily upon one hemisphere or the other, and these differences were in the expected directions in grouped data, but in a given subject could show even opposing asymmetries on repeated measures. In these studies the most consistent grouped data left-right hemisphere difference measures were those related to the speech CNV and the peak amplitudes of word evoked potential components in the 100 to 200 msec latency range. Inspection of the raw data, however, revealed that even these showed marked variability in left-right amplitude ratios from sample to sample.

There is almost no information in the available literature on the subject of correlations between slow potential phenomena such as the CNV, other event related potential parameters and the ongoing EEG. Curry (1977) examined the relationships between scalp recorded slow potential fluctuations and event related potentials in an auditory discrimination task but found that there were very few consistent relationships among the measures. The correlations which he did find were between CNV measures and evoked potential amplitudes.

Our failure to demonstrate any significant interrelatedness among our various electrophysiological measures, many of which have been shown to vary in left-right symmetry as a function either of presumed cerebral dominance for language or verbal vs. nonverbal task requirements, underscores a problem encountered by all researchers in the general field of cognitive science, and particularly by those employing electrophysiological parameters as indicators of higher order cerebral processes: in experiments with human subjects it is extremely difficult, if not impossible at a given moment in time, to specify and isolate a single cerebral process.

It appears to us that different electrophysiological parameters reflect different aspects of the left-right and within-hemisphere organization of the two halves of the brain. The data obtained in this work support the concept that the normally functioning integrating brain participates in a more broadly based and less stereotyped fashion (in the processes indexed by our electrophysiological measures) than either anatomical (Geschwind and Levitsky, 1968; Wada and Davis, 1977) or clinical dysfunction evidence (Milner, 1974) has been taken to suggest.

The second main conclusion is that as a group children with the minimal cerebral dysfunction syndrome do differ significantly from age-matched normal controls with respect to certain electrophysiological measures.

A similar general observation has been made by several other investigators including Low and Stoilen, 1973; Kinsbourne, 1973; Satterfield and Braley, 1977; John et al., 1977; Fuller, 1977 and Rebert et al., 1978, based upon demonstration of frequency, latency or amplitude abnormalities in either the EEG or event related potential parameters in groups of children with learning disorders or the MCD syndrome. While there are scattered references in the existing literature to differences in EEG L/R symmetry measures between normal and learning disordered children, only one other group of investigators (John et al., 1977) has systematically explored intrahemispheric differences in cerebral electrical activity in this context.

In an ongoing study which now includes a large number of subjects, John and his colleagues have used a form of cluster analysis to differentiate not only abnormal (MCD or learning disabled) children from normals, but to distinguish between different kinds of learning disability. However, their methods of data acquisition and analysis preclude any direct comparison with the regional differences we have found between our normal and MCD subjects. It should be noted that while John et al. depend very heavily upon psychometric testing for diagnostic classification, we have found that psychological data is less reliably related to an overall diagnosis than either neurological examination or elements of an organic behavior syndrome.

The work that we are reporting here has shown that the single most potent measure discriminating MCD from normal children is the difference in magnitude of the early segment speech CNV between anterior and midtemporal sites in the right hemisphere, with the MCD children having greater differences (or more localized potential distribution over the scalp) than normal children. The same kind of intrahemispheric differences were shown for mid-latency components of evoked responses to visually presented word stimuli while both speech CNVs and pattern reversal visual evoked potentials were more asymmetrical between homologous brain regions in MCD than in normal children. All of these event related potential measures were better "indicators" of the MCD diagnosis than EEG frequency analysis although our finding of greater slow activity in MCD children than normals is consistent with the observations of many other investigators. Some other very recent evidence (Shagass et al., 1978; Neville et al., 1978; Kurtzberg and Vaughan, 1978) has also demonstrated that differences in scalp distribution of event related potential measurements can provide significant diagnostic or discriminating information when comparing normal and abnormal subjects.

The possibility of artifact contamination must be considered in any explanation of our findings. Szirtes and Vaughan (1977), while admitting that the CNV paradigm might be the one possible way to avoid extra-cerebral artifact in such experimental studies, have argued that slow potential asymmetries preceding speech are most likely due to variations in the glosso-kinetic potential. Grozinger et al. (1977), in turn, have categorically stated that Szirtes and Vaughan were recording skin potentials or galvanic skin responses rather than glosso-kinetic, palate or pharyngeal muscle activity. While we always monitor the electro-oculogram (our computer controlled system automatically discards any trial from the average which is contaminated by even the slightest eye movement) we have only intermittently used recording of glosso-kinetic potentials to determine their possible contribution to the electrical activity recorded from anterior head regions. While we cannot agree with Grozinger et al. that the slow potentials observed by Szirtes and Vaughan must all be generated in the skin, neither can we agree with Szirtes and Vaughan that glosso-kinetic potentials account for most or all of the slow potential asymmetries which we have observed. In the absence of any physiological or anatomical evidence, we find it very difficult to credit their argument that asymmetrical tongue movements are related to language dominance. When we have employed glosso-kinetic potential recording we have found these potentials to be much shorter in duration and closer to the time of articulation than our early segment speech CNV, and furthermore they were almost never asymmetrical. We believe that the most parsimonious explanation of our data is that the early segment speech CNV is in fact a cerebrally generated potential.

Another possible source of contamination of our data, particularly with the electrode placements used, is lateral eye movement. It is well known that reading, as required by our speech CNV paradigm, may be associated with saccadic eye movements which, in turn, are associated with event related potentials in the brain. As indicated above, we have very carefully controlled for EOG artifact in our recording procedures. Close inspection of individual word evoked responses reveal that while they are often asymmetrical with higher amplitude on the right side than on the left, their various components are in phase over the two hemispheres. If these were being generated by or significantly influenced by lateral saccades (since we employed a contralateral ear reference), the potentials would often or always appear to be more or less equal in amplitude but up to 180° out of phase over the two sides. The possibility remains that what we are recording as word evoked potentials may be brain potentials related to very small saccadic eye movements.

Whatever the final explanation for the asymmetries and lateralization differences observed, these studies have clearly demonstrated that MCD children as a group show greater lateralization/localization over the scalp as compared to normals. This appears to be

particularly true for potentials presumably related to visual function, reading and language generation. It is possible that these findings are a reflection of less than normal cerebral integration in the minimal cerebral dysfunction syndrome, and this may be one reflection of the as yet completely unknown pathophysiology of this disorder.

SUMMARY

A comprehensive test battery including a number of neurophysiological measures for assessment of hemisphere activity during reading, speech and other tasks presumed to engage primarily in the left or right hemisphere has been applied in a study of twenty-nine normal children and sixteen with the minimal cerebral dysfunction syndrome. The electrophysiological measures included the speech CNV, evoked potentials to visually presented word stimuli, alpha frequency power spectra at rest and during left and right hemisphere tasks and pattern reversal visual evoked potentials. Correlations and multivariate analysis of the data (including stepwise regression and principal component analysis) showed no consistent intrahemispheric correlations among the different measures. MCD children showed significantly greater intrahemispheric and interhemispheric ratios than normal children.

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HEMISPHERE DIFFERENCES IN EVENT RELATED POTENTIALS AND CNV'S
ASSOCIATED WITH MONAURAL STIMULI AND LATERALIZED MOTOR RESPONSES

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INTRODUCTION

Hemispheric lateralization of cerebral processing of various kinds is well established, but the electrophysiological concomitants of such lateralization have proved more difficult to demonstrate. In the auditory system the principal projection is accepted as being to the temporal cortex contralateral to the stimulated ear, but with secondary projection to the ipsilateral temporal cortex. Lateralized motor responses are, of course, even more clearly a function of the motor cortex contralateral to the responding limb.

Lateral evoked potential differences to auditory stimuli have been studied primarily with respect to the N1 or N1/P2 components. The N1 component has been generally accepted as the peak negative deflection occurring in the period 80 to 140 msec after an auditory stimulus and as reflecting the processes of selective attention. Its amplitude, either with respect to baseline or to the following P2, is largest at or near the vertex and diminishes progressively in all directions from that point (Vaughan and Ritter, 1970; Kooi et al., 1971; Picton et al., 1974). However, Vaughan and Ritter have suggested that its real origins are from dipole sources located in the temporal lobes and that the apparently larger amplitude seen at the vertex is merely the effect of summation there of volume conducted signals from the two temporal sources. They also noted in four subjects that N1 showed a slight contralateral predominance to monaural stimulation. Similarly increased contralateral amplitudes for N1 were reported by Tanguay et al. (1977); Hink et al. (1978); Wolpaw and Penry (1975; 1977). The last named authors noted that, in addition to the usual vertex N1 component at 105 msec, there was a second biphasic component at T3 and T4 which was more

asymmetric than the first and had a latency of 105-110 msec for the initial positive wave and of 150-160 msec for the following negative wave. A number of reports suggest that apart from the contralateral effect there is also a tendency for there to be a right hemisphere amplitude predominance (Peronnet et al., 1974; Tanguay et al., 1977; Mononen and Seitz, 1976). However, not all studies confirm the contralateral effect. Picton et al. (1974) report that N1-P2 distribution is the same whether stimulation is monaural or binaural, and Hasland (1974) and Mononen and Seitz (1976) report no lateral predominance to monaural stimuli. There have also been several studies which have reported shorter N1 latencies over the contralateral hemisphere (Wolpaw and Penry, 1975; Butler et al., 1969; Spreng, 1971).

Lateralized electrical changes associated with motor tasks have been a little better established. A clearly lateralized motor cortex potential accompanies movement of a contralateral limb and the slow Bereitschaftspotential which precedes voluntary movements is found to be slightly larger over the hemisphere contralateral to the responding limb. On the other hand the CNV, which occurs during warned foreperiods, has not shown consistent asymmetries although there have been one or two reports of minor asymmetries over central regions, the larger amplitudes being held to occur either over the hemisphere contralateral to the responding hand or over the speech dominant hemisphere when an appropriate task was employed (Butler and Glass, 1971, 1974; Otto and Leifer, 1973; Low et al., 1976; Rohrbaugh et al., 1976; Curry et al., 1978).

The present study investigates hemisphere involvement in auditory processing and in preparation for motor response. It was hypothesized that asymmetries would be found in EP and slow potential components depending on the ear of stimulation and the lateralization of motor responses and that the relatively long latency range normally allocated to evoked potentials referred to as N1 might be concealing the fact that more than one component was occurring during this period. Given that the existence of two or more components could be established it was hoped, by studying their relative distributions, to shed more light on the systems involved and their functions.

METHOD

Evoked Potential-CNV Paradigm

Eighteen subjects, seven male and eleven female, were tested. Twelve subjects classed themselves as right-handed and six as left. Each subject was required to listen to a series of trials in which a 30 msec warning tone was followed 1.5 sec later by a 500 msec

1000 Hz tone. The warning tone could be either high (1600 Hz) or low (600 Hz), and all stimulus pairs were delivered monaurally. The high and low warning tones and the ear of stimulation were varied according to a pseudo-random sequence which was the same for all subjects. Subjects were instructed that if the warning signal was high they were to terminate the following 1000 Hz tone as rapidly as possible by pressing a button with the hand ipsilateral to the stimulated ear. If the warning signal was low they were to use the button in the hand contralateral to the stimulated ear to terminate the 1000 Hz tone. Stimuli were delivered at approximately 60 dB to each ear. All subjects had normal hearing in the frequency ranges used and all reported that the intensity of stimuli was subjectively equal in both ears.

During the task, evoked potentials and slow potential changes were recorded from Ag/AgCl electrodes located at positions Fpz, T3, T4, T5, T6, C3, C4 and Cz of the international 10:20 system. Lateral electrodes were referred to the contralateral mastoid process; Fpz was referred to the right mastoid, and Cz was referred separately to both left and right mastoids. Further pairs of electrodes on the forearms recorded the EMG to button pressing.

Primary recording was by a modified 16 channel Elema-Schonander Mingograph using 5 sec time constants and 70 Hz filters. Two second epochs of time, starting 100 msec before each warning tone, were sampled for all channels and stored by a PDP-12 computer on digital tape at a resolution of 8 msec per point. Subsequently averages were computed for twenty trials of each of the following four conditions: (1) Left ear stimulation - left hand press; (2) Right ear stimulation - right hand press; (3) Left ear stimulation - right hand press; (4) Right ear stimulation - left hand press. Reaction time (RT) was recorded on each trial, and mean RT values were calculated for each of the four conditions. Trials on which there was excessive eye movement or other artifact were rejected on-line.

The same experimental paradigm was also presented to one patient in whom intracerebral gold electrodes had been implanted for therapeutic purposes. The presence of high amplitude, infra-slow activity at these electrodes necessitated the use of a relatively short (0.6 sec) time constant in this case. Recording was from an anterior-posterior array of electrodes located subdurally over the fronto-temporal regions of the right hemisphere and from selected electrodes in the depths of the frontal lobes. Each electrode was 150 microns in diameter and 4 mm long.

Subjects' lateral preferences were assessed using the Edinburgh Inventory (Oldfield, 1971), and measures of auditory lateralization were made using a dichotic listening task which required them to listen to sequences of six digits presented in pairs from pre-

recorded tape. The two digits of a pair were presented simultaneously, one to each ear. The task was to repeat as many as possible of the six digits after each sequence. Two balanced sets, each of twenty-five groups of six digits were presented. The headphones were reversed between the two sets to control for any possible intensity differences or instrumental inequalities. Three measures were used: (1) a percentage difference of correctly reported digits for each ear; (2) a measure of ear reported first; (3) a measure of absolute performance (i.e., percent correct irrespective of ear).

Evoked Potential Paradigm

Based on the results of the experiment already described, a further ten subjects were tested in various auditory paradigms to determine more precisely the latency and distribution of the auditory EP components seen and the validity of using the contralateral mastoids as reference. Each subject received minimally two series of 30 msec, 1000 Hz 60 dB tone pips delivered irregularly at a mean rate of one every 4 sec to left, right or both ears in a pseudo-random sequence. To one series he listened without responding, and to the other he pressed immediately a button with the hand ipsilateral to the stimulated ear, making no press if the stimuli were binaural. In one subgroup of five subjects electrodes were located at C3, C4, T3, T4, A1 and A2 and were referred (a) to a balanced noncephalic reference as described by Stephenson and Gibbs, 1951; Lehtonen and Koivikko, 1971; Wolpaw and Penry, 1975), (b) to the tip of the nose, and (c) to contralateral mastoids. Oculograms were recorded from electrodes at the nasion and right outer canthus. In the remaining subjects further electrodes were added to give a complete coronal chain with 10% interaural spacing, plus left and right neck electrodes 10% below the pre-auricular level, together with Fp1, Fp2, F7, Fz, F8, T5 and T6. Recording conditions were otherwise as described for the first experiment.

RESULTS

Measures and Analysis

Preliminary analysis of the time interval normally attributed to the N1 response revealed three negative components with differing distributions which we have defined as peak negative values in the following latency brackets: N1a (60-90 msec), N1b (95-115 msec) and N1c (116-150 msec). Latency and amplitude measures were made for each of these components together with N2 and P3. Three measures of CNV amplitude were made: early CNV - from 400 to 950 msec after S1; late CNV - from 950 to 1500 msec after S1; 'standard' CNV -

from 1300 to 1500 msec after S1. Each measure was expressed as a mean value for the period concerned. Difference measures were calculated for each component measure at homologous electrode sites (e.g., T3-T4). Additionally a more general hemisphere asymmetry score was calculated by summing the difference scores for all homologous electrode pairs. All amplitudes were measured with respect to a baseline calculated as the mean amplitude level over the 1.0 sec prior to S1.

All primary measures were initially analyzed using a four-way ANOVA (sex X hand X electrode X condition). Where permissible separate one-way ANOVAs were performed to illuminate the main effects. A posteriori contrasts were made using a Duncan multiple range test. Significance levels for these and all subsequent procedures were $p < 0.05$. Pearson product moment correlations were performed on selected pairs of variables. The CNV measures were subjected to a stepwise discriminant analysis (SPSS Version 7) in an attempt to discriminate the experimental conditions.

EP-CNV Paradigm

Evoked potentials. N1a appeared primarily at the temporal electrodes and at Fpz with a mean latency to peak over all electrodes of 75 msec. Its mean latency diminished anteriorly, being shortest at Fpz and longest over central regions where it was only measurable on about half of the averages, usually as a slight inflection on the ascending part of the second negative-going component (N1b). N1a was larger in the left hemisphere of right-handed subjects and in the right hemisphere of left-handed subjects. Its amplitude was approximately -5 to -7 μV in anterior and temporal areas, but was, when measurable, more variable over central regions where it could range from -4 to more than -15 μV .

N1b had a mean latency of 106 msec and was distinguished as a separate component both on the basis of its later occurrence and its distribution. It was measurable most consistently over central electrodes where its mean amplitude was -16 μV . At temporal electrodes it was measurable on less than half the averages and at Fpz on only one sixth. At C3 and C4, amplitudes were larger over the hemisphere contralateral to the stimulated ear, but this difference failed to reach significance. However, amplitude asymmetries were significantly related to handedness, larger values being associated with the hemisphere contralateral to the preferred hand, particularly in the left-handers. Latencies showed no clear distribution pattern but were significantly shorter in the hemisphere contralateral to the preferred hand. At C3 and C4 there was also a significant relationship between N1b latency and the hand used for response; the shorter latency was at the contralateral electrode.

The third negative component (Nlc) had a mean latency of 129 msec and was significantly larger over the hemisphere contralateral to the stimulated ear. It was measurable on 82% of the averages from temporal electrodes and 75% of averages from Ppz, but on only 50% of the averages from central electrodes, where it could appear either as an extension of Nlb or as a separate peak. Nla amplitudes were also significantly larger and latencies significantly shorter in the hemisphere ipsilateral to the preferred hand. Although this component was seen most consistently over temporal regions its mean amplitude at temporal electrodes was approximately $-8\mu\text{V}$ compared with -13 to $-16\mu\text{V}$ at central electrodes. At first it seemed possible that Nlb might be the result of a fusion of the Nla and Nlc components, but this proved to be unlikely as in many instances all three negative peaks could be separately distinguished at the same electrode.

The N1 series of components was followed by the usual P2, N2, P3 complex, the mean latencies being 182, 226 and 302 msec, respectively. No significant hemisphere effect was found for N2; P3 showed a slight predominance contralateral to the ear of stimulation, but this did not reach significance. P2 showed consistently higher mean amplitudes contralateral to the ear of stimulation. Mean hemisphere differences were in the order of $1-2\mu\text{V}$, but we are at this stage unable to say whether this difference is significant.

In addition to the condition and hand effects, some sex differences emerged. Males showed significantly larger amplitudes for components Nlb, Nlc and N2 and females for P3. Females also showed significantly shorter latencies for Nla.

Fig. 1 a-d illustrates averages across all subjects of the waveforms elicited by the four conditions. Fig. 2 gives in histogram form the amplitude values for each of the components measured in each of the experimental conditions, including amplitude differences between homologous electrode pairs.

CNV

The group as a whole produced "normal" CNVs, the mean vertex amplitude for the late and standard CNV measures being $-15\mu\text{V}$. Asymmetries of late and standard CNV measures were noted between homologous electrode pairs, these being highly significant between C3 and C4. The larger amplitudes were found over the hemisphere contralateral to the responding hand. Examination of subgroups showed that asymmetries were significantly larger when subjects used their preferred hand, particularly in left-handers and in the ipsilateral press condition. Late CNVs were significantly larger in females than males.

The early component of the CNV was seen prominently at Fpz. It was present, and relatively symmetrical over central and temporal regions, diminishing posteriorly to $-1 \mu V$ at T5 and T6. Early CNV amplitude showed no consistent relationship to the hand used for pressing but showed a similar relationship to handedness as that displayed by the late CNV.

Performance. Mean reaction times (RT) for the four conditions were: (1) Stim. left/Press left: 186 msec; (2) Stim. right/Press right: 190 msec; (3) Stim. left/Press right: 203 msec; (4) Stim. right/Press left: 195 msec. RT in condition 3 was significantly different from that in the other conditions, but overall RT showed no significant correlations with any of the CNV or EP measures.

Lateral preferences. The mean Laterality Quotient (LQ) for the right-handers, assessed by their scores on the Edinburgh Inventory, was +85, and for the six left-handers the mean LQ was -64 and confirmed subjects' self-reports of handedness.

The first dichotic listening test measure was based on a percentage difference between reported digits in the right and left ears. The mean score for the group was -29 indicating a moderate right ear advantage. It was, however, only possible to administer the test to twelve subjects, of whom eight showed a right ear advantage, two a left ear advantage and for two the difference was zero. The second measure indicated that right ear digits were reported first by nine subjects and left ear digits by three subjects. No clear relationship to handedness emerged. The mean level of correctly reported digits was 77%, males performing significantly better than females in the ratio of 91%: 70%. Neither of the ear advantage measures was significantly related to any of the other experimental variables.

EP Paradigm

The results from the second phase of the experiment confirmed the contralateral predominance of N1b and N1c and the distributions of components as seen in the first phase of the experiment (see Fig. 3). The improved resolution (2 msec per point) permitted more accurate measurement of latencies of the three principal negative components which emerged as : -N1a: 60-78 msec; N1b: 90-104 msec; N1c: 118 msec. The additional electrodes at Fp1; Fp2; F7 and F8 also confirmed the frontal, as well as temporal, distribution of N1a.

The three different references used in this study produced very similar results. From Fig. 3 it can be seen that the noncephalic and contralateral mastoid references produce the closest correspondence in both waveform and amplitude. Reference to the nose



Fig 1a

Fig 1b

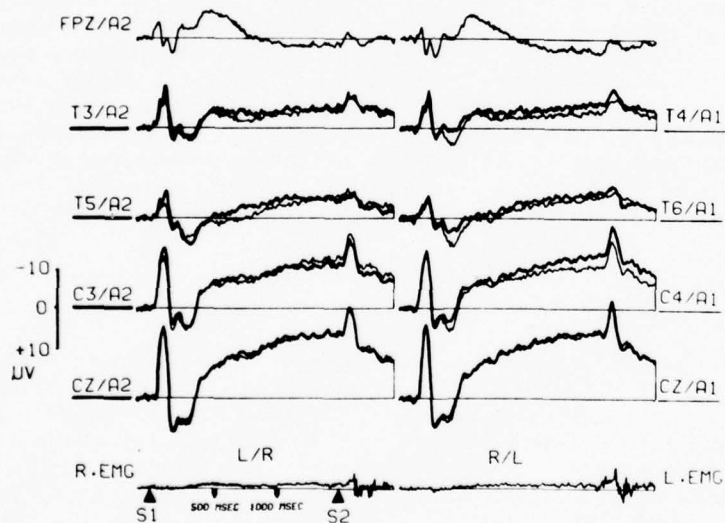


Fig 1c

Fig 1d

Fig. 1. Averages across all subjects and all conditions. Thickness of line indicates the electrode from which each trace of a pair is derived. The ear of stimulation followed by the hand of response are indicated immediately above the EMG trace for each of the four conditions.

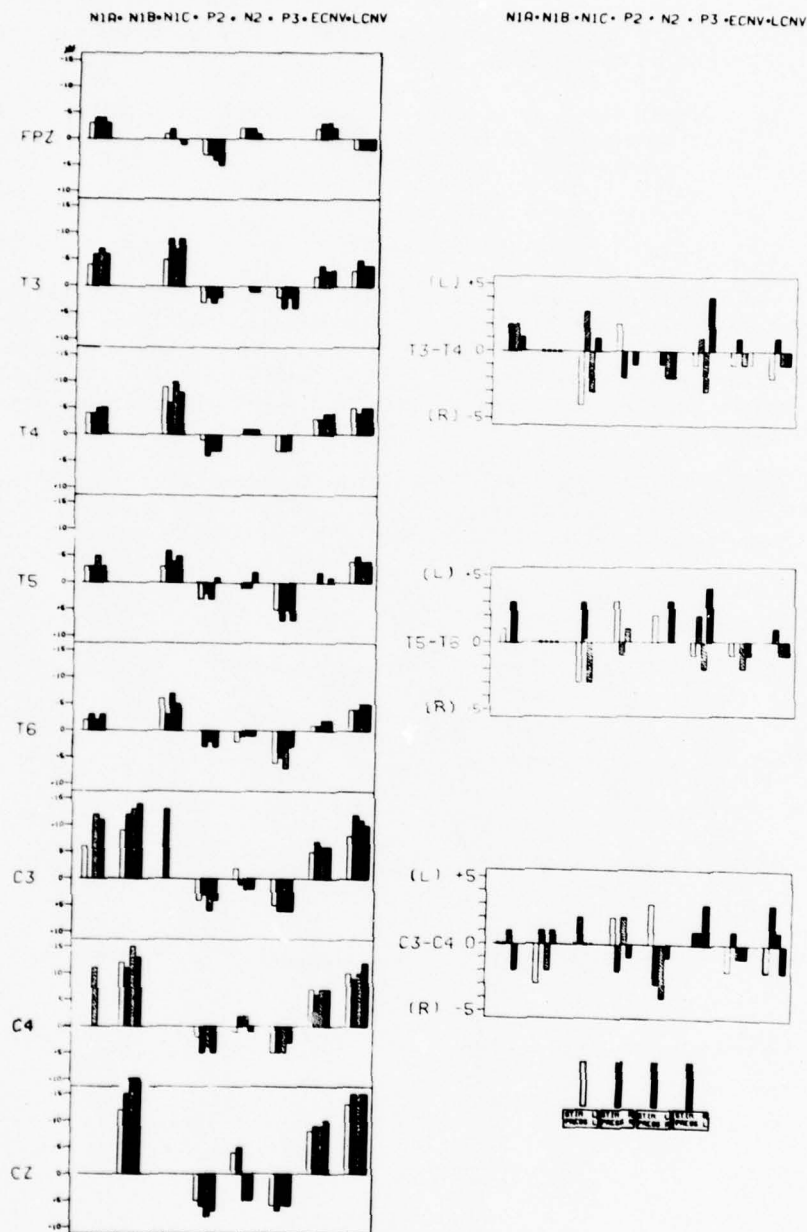


Fig. 2. Histogram bars show mean amplitude of each component for each condition across all subjects. On right are amplitude differences between homologous pairs of electrodes.

resulted in very slightly lower amplitudes and a tendency for the N1a component to disappear.

The coronal chain of electrodes used showed no reversal of the N1 series of components below the level of the Sylvian fissure as reported by Vaughan and Ritter (1970).

Intracerebral Evidence

Recordings were made from the patient with intracerebral gold electrodes using both the original paradigm and the later higher resolution EP paradigm. The electrodes displaying the most prominent auditory EPs were those on the cortical surface of the right hemisphere and five electrodes close to the orbital surface of the right frontal lobe.

Although CNVs could be discerned at a number of sites in the EP-CNV paradigm, the relatively short time constant used and the presence of infra-slow activity made their evaluation uncertain.

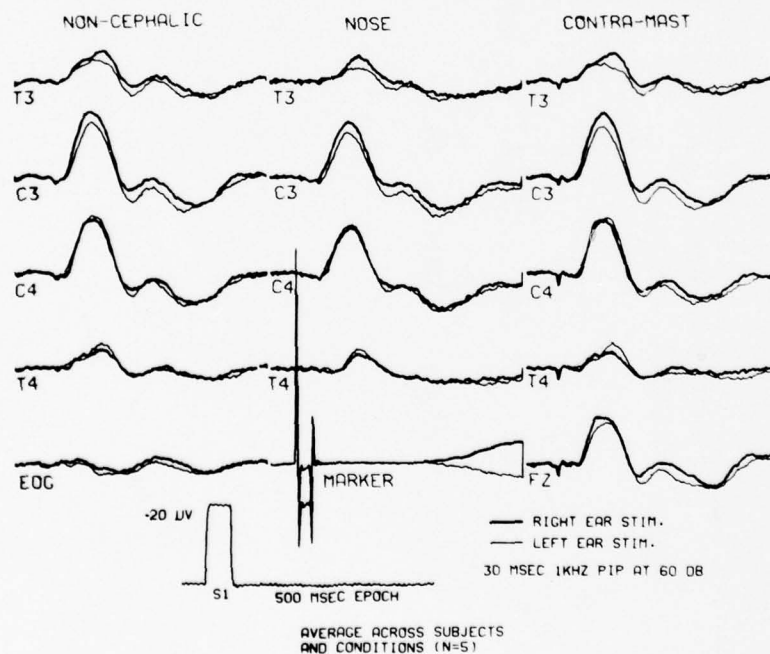


Fig. 3. Comparison of balanced noncephalic, nose and contralateral mastoid references for simultaneously recorded averages across five subjects.

EPs at the cortical electrodes displayed a positive component with peak latency at 84 msec, a prominent negative component peaking at 136 msec and a later positive complex with a peak latency of 188 msec. In the EP-CNV paradigm the negative peak tended to be larger in amplitude to left ear (i.e., contralateral) than to right ear stimulation. In the orbital regions of the frontal lobe the most medial electrode, 64, showed an EP complex generally similar in form and latency to that seen at the superior cortical electrodes. Other evidence suggested that this electrode was in orbital gray matter. The four other electrodes examined showed a waveform which was virtually phase reversed with respect to those at the cortex. These electrodes were thought to be adjacent to the lower orbital cortical layers, probably in white matter. The latencies of the principal components were approximately 16 msec shorter to left than to right ear stimulation (see Fig. 4).

DISCUSSION

The first of the hypotheses tested, namely that longer latency evoked potentials to monaurally presented stimuli would show an amplitude predominance over the contralateral hemisphere has received clear support from the study. Both the N1b and N1c components show this asymmetry, and there are indications that it may be present to a lesser extent for P2 and P3. There have, however, been indications in some of our pilot and ancillary studies that this asymmetry can vary substantially with rate of stimulus presentation, and stimulus characteristics and is influenced by the inclusion of a motor response.

The second hypothesis tested, namely that the component frequently referred to as N1 is not a simple discrete entity but is composed of at least two separate elements, received support. Three relatively independent components have emerged: the fronto-temporal N1a with a predominance over the hemisphere contralateral to the preferred hand, the central N1b which seems to approximate most closely to what is usually regarded as the vertex auditory response and N1c which is prominent temporally.

What function is reflected by the N1a component is difficult to determine. The slight predominance in the left hemisphere of right-handers and in the right hemisphere of left-handers suggests that it may be sensitive to lateral preference. It is of particular interest that it is one of the few late EP components to have a frontal rather than a centro-parietal distribution. In their outline of the scalp topography of auditory EPs, Goff et al. (1977), using binaural stimulation, distinguished a negative component at 75 msec the distribution of which was similar in many respects to that of N1a. They speculated that this component might be myogenic

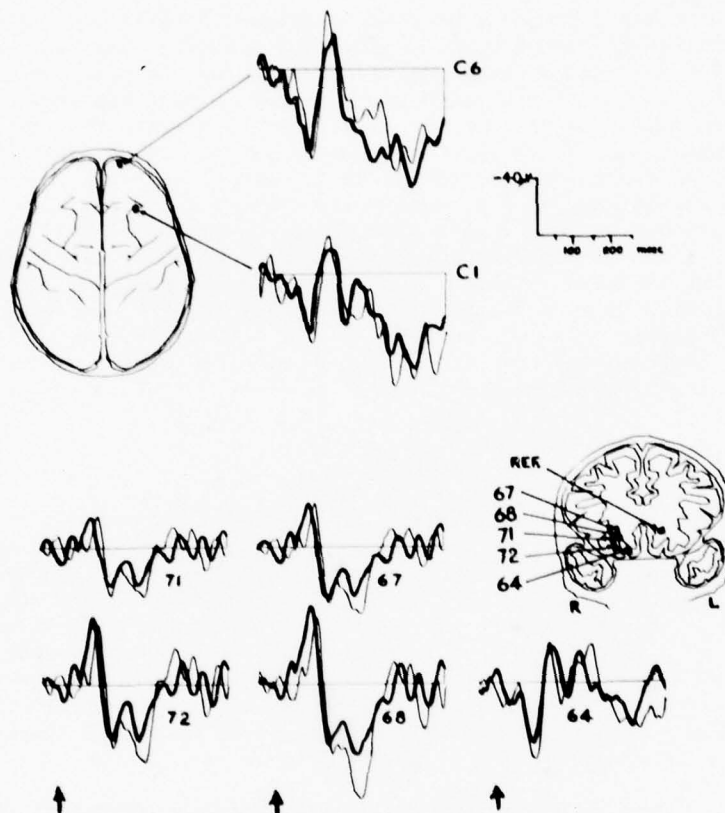


Fig. 4. Evoked potentials recorded intracerebrally to 60 dB monaural tone pips in one female patient. Dark trace indicates right ear stimulation, light trace left ear stimulation. Each trace is an average of forty trials.

in origin. However, all our evidence points to the fact that N1a has cerebral origins. There are some early indications that it appears most consistently when stimuli contain information about the side of response - whether immediate or delayed. Another feature linking it with the selection of the side of response is the fact that it is significantly larger in amplitude in the hemisphere cross-over conditions (3) and (4).

The distribution and amplitude of N1b indicated a central predominance, although the relatively constant latency pattern suggested its dependence upon more general activation from lower

systems. Like N1a it tended to increase in amplitude in the cross-over conditions (3) and (4). Its amplitude predominance in the hemisphere contralateral to the stimulated ear and its shorter latency in the hemisphere contralateral to the hand selected for response might suggest that it plays a key processing role between stimulus and response.

N1c is probably the same component as that identified by Wolpaw and Penry (1970) as the Tb component of their T complex. Its latency is slightly shorter than that originally attributed to Tb, but Wolpaw and Penry regarded this as lengthened by the filters used in the early experiment. They report that recording with a different filter decreased latencies by 10-15 msec. We discerned no consistent positive component at T3 and T4 which could be equated with their Ta component. However, we noted that in subjects with a prominent blink potential the positive peak of that potential had a latency of about 95 msec and could be seen in an attenuated form at T3 and T4. It would seem that in any experiments in which Ta is to be studied as one of the variables, adequate control for eye movements should be a prerequisite. The origins and distribution of N1c are still far from clear. We would wish to view it as predominantly temporal by virtue of its higher incidence in those regions and its significantly larger amplitudes and shorter latencies contralateral to the stimulated ear. However, on those occasions when it could be recorded over central regions the mean amplitudes there were larger and the mean latencies shorter than elsewhere. It is possible that this apparent anomaly could be explained by a strong sequential dependency upon the immediately preceding large N1b component almost invariably seen in such cases. This is to some extent a measurement problem which will require resolution in future experimentation.

The previously reported general tendency for a right hemisphere amplitude predominance of N1 was not confirmed by this study. The only consistent pattern across homologous electrode pairs was for N1a to be slightly larger in the left hemisphere, the mean value of this asymmetry being 0.8 μ V. N1b was the only component to show a mean asymmetry favoring the right hemisphere, but this occurred at temporal electrodes only; C3-C4, where the component was largest, showed a slight left hemisphere predominance (0.5 μ V).

The study provides no support for the Vaughan and Ritter (1970) view that the vertex auditory response is a simple summation of volume conducted signals from dipole sources in the temporal lobes. The principal temporal component is of a longer latency than the principal vertex component, and we failed to find any convincing evidence of polarity reversals occurring below the level of the Sylvian fissure. Our evidence suggests that in some subjects the nose constitutes an active electrode and that this is the most

likely explanation of those cases in which reversals have previously been reported.

The experimental paradigm used produced the most consistent, if relatively small, lateralization of the CNV that we have so far encountered. Both the "standard" and "late" CNV amplitude measures showed this asymmetry, the higher amplitude being over the hemisphere contralateral to the responding hand. This was most prominent over the central electrodes but could also be seen to a smaller degree over temporal locations. In this respect it contrasts with the asymmetries seen in the Bereitschaftspotential (BP) which precedes voluntary movement. Although lateralized over central and motor areas in conditions of unilateral pressing, BP asymmetries are not generally reported over temporal areas. The results of the stepwise discriminant analysis produced a discriminant function based primarily on central CNV measures which were particularly effective in identifying conditions by hand of response, but less effective in identifying them by ear of stimulation.

In a subsequent analysis in which the four conditions were reduced to two, based only on hand of response, the discriminant function obtained successfully classified 80% of the cases.

The paradigm chosen for the experiment emerged as a useful one for distinguishing those electrophysiological phenomena associated with processing the auditory warning signal from those concerned with preparation for the motor response. The amplitude picture would suggest that up to and including the P300 the system is evaluating the information contained in the warning signal and that processing predominates in the hemisphere more directly connected with the sensory organ, i.e., the hemisphere contralateral to the stimulated ear. Thereafter the hemisphere concerned with the motor response tends to predominate. When the hand ipsilateral to the stimulated ear is to be used both kinds of processing remain in the same, contralateral hemisphere. When the hand contralateral to the stimulated ear is to be used the transfer from the sensory to the motor hemisphere is reflected in a crossover of the rising negative shift such that it ultimately predominates in the hemisphere contralateral to the hand to be used. Nevertheless the latency pattern of N1b, and its ability to indicate the hand due to be used for pressing, argue against taking too simplistic a view of the stage at which the major responsibility for processing passes from one hemisphere to the other.

SUMMARY

Eighteen subjects with scalp electrodes and one patient with intracerebral electrodes were tested in a warned foreperiod reaction time paradigm in which S1 was a high or low monaural tone pip which indicated whether the ipsilateral or contralateral hand was to be

used to respond to S2, a tone of intermediate frequency presented 1.5 sec after S1.

A further group of subjects was tested with monaural and binaural stimuli in both passive listening and immediate response situations recording from a coronal chain of electrodes with three different references.

The evoked potentials to S1 in the latency bracket of 60-140 msec were found to consist of three distinct components: an early fronto-temporal component, a middle latency central component and a later, essentially temporal component, the last two predominating over the hemisphere contralateral to the stimulated ear. No support was found for the view that vertex auditory responses are simple summations of temporal lobe responses.

The CNV which developed between S1 and S2 was of significantly higher amplitude over the hemisphere contralateral to the hand required for response.

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DIFFERENT VARIANTS OF ENDOGENOUS NEGATIVE BRAIN POTENTIALS IN
PERFORMANCE SITUATIONS: A REVIEW AND CLASSIFICATION

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INTRODUCTION

After the discovery of the CNV (Walter et al., 1964), the existence of many other, mainly endogenous negative shifts have been claimed in different situations. The common feature of these ERPs is their unclear relationship to the original CNV and, of course, to each other. The present paper attempts to list these negative shifts and shed some dim light on the question of their mutual relationships.

ENDOGENOUS NEGATIVE POTENTIALS AS SEPARATED
MAINLY ON THE BASIS OF SITUATION OR PERFORMANCE

CNV, readiness potential, SI-related slow negativity. In 1965 the existence of a long-duration premotion negative shift called Bereitschaftspotential (readiness potential, RP), quite closely resembling the CNV, was reported (Kornhuber and Deecke, 1965). Thereafter these two negativities have lived in peaceful coexistence and mutual respect, often being studied without the necessary methodological and theoretical integration. Every now and then the question of their mutual relationship was, however, raised mainly because of their conspicuous similarities. Both are negative shifts of quite long duration. Both have a central focus approximately at the vertex. RPs show a clear asymmetry, with a larger amplitude contralateral to the responding limb (this difference being maximal over the respective motor area); this asymmetry starts during the long negative ramp several hundreds of milliseconds before the EMG onset (Deecke and Kornhuber, 1977). Many CNV studies have also shown such an asymmetry, but less clearly (for a review,

see Donchin et al., 1978). RPs only exist during preparation for a movement, whereas the latter condition has proven ideal for eliciting a CNV. In fact, there has been some dispute as to whether a CNV can ever be completely nonmotor (see Donchin et al., 1978). Many of the factors affecting the amplitude of the CNV also affect the amplitude of RPs, such as motivation (for a review emphasizing these similarities, see McAdam, 1973).

Besides (1) the eliciting paradigm (and the often larger amplitude of the CNV), there have been at least the following two important differences between the two shifts: (2) A morphological difference: whereas RPs show a ramp-like rise, the CNV often develops abruptly; (3) A topographical difference: contrary to RPs, the CNV usually has a high frontal amplitude especially when measured at an early phase. It appears to be mainly due to these three differences that the two shifts have been kept that separated. However, quite recently data were obtained that suggested the existence of an S1-related fronto-central slow wave, with a sharp onset, which often overlaps the S2-related slow wave ("true CNV") in the CNV paradigm (e.g., Loveless and Sanford, 1974; Gaillard, 1976). Consequently, as the latter two differences (2-3) were, in fact, attributed to another wave, usually called the "orienting component of the CNV", some workers suggested that the residual S2-related slow potential is, in fact, an RP (e.g., Gaillard, 1976; Rohrbaugh et al., 1976). Hence the original CNV would be composed of an orienting component and RP. Such thinking was supported by data indicating artificiality of paradigm differences, e.g., it has been shown that a CNV can exist with no S1 and S2 and that an RP can exist during the S1-S2 interval.

There is, however, one weak loop in this reasoning. The evidence that the S1-related fronto-central slow wave is separable from the S2-related slow wave is strong - though calling it an orienting component appears to be premature. On the other hand, the role in RPs of a "true CNV"-type widespread, central, nonspecific, negative shift (Syndulko and Lindsley, 1977) associated with motivation, preparation, expectancy, etc., i.e., with increased activity, appears likely. It is possible that the RP is a hybrid wave consisting of (1) the CNV and (2) some slow negative potential specific to response initiation (Hillyard, 1973). The first possibility (1) is supported by data showing that the RP is affected by similar variables as the CNV (McAdam, 1973). Interestingly, even the scalp distribution of the RP shifts anteriorly (and hence becomes more CNV-like) under the influence of such variables (McCallum, 1978). Moreover, usually the Cz amplitude is larger than that above the contralateral hand area (in manual tasks), and the amplitude above the ipsilateral hand area is substantial (e.g., Syndulko and Lindsley, 1977). It might well be that even in a most boring RP situation with frequent repetitions of a movement there

still is some CNV-inducing element left - a movement is some activity, something to do and concentrate on, after a period of inter-trial silence and rest.

As to the second possibility (2), the aforementioned contralateral hemispheric asymmetry is well established. This asymmetry starting well before the onset of the movement speaks in favor of the existence of some negative shift specific to response initiation. This shift, as such, may be of a relatively low amplitude. Hence, the negative shift known as RP is suggested to be composed of a low amplitude motor-specific slow negativity and of a CNV of varying amplitude.

What, then, is the traditional CNV? Besides the "true CNV" defined above, it appears to be composed of an S1-related slow negative wave and, when a motor task is involved, a slow negativity specific to response initiation. The latter component is lent credence by hemispheric asymmetries contralateral to the responding limb found also in the CNV paradigm (Donchin et al., 1978). The S1-related component (appearing mainly with an auditory S1) might reflect the arousing and facilitatory properties of a stimulus (Loveless and Sanford, 1974; Gaillard, 1976; Gaillard and Naatanen, 1976), probably activation of some reticular and thalamic activation systems. The S2-related negative shift ("true CNV") is somewhat more posterior and, presumably, is also related to the activation of such nonspecific systems (Naatanen, 1967). [Skinner's (1971) cryogenic lesion studies have identified frontal and central negative shifts having separate relations with the thalamus.] This activation is presumably associated with sustained activity required between S1 and S2 (e.g., preparation for a task performance). Additionally, there may exist during the S1-S2 interval some modality-specific slow potentials (Gaillard and Naatanen, 1976; Syndulko and Lindsley, 1977) and some other function-specific potentials such as those associated with word and pattern processing (Rebert et al., this conference).

Speech-related negativity. A number of studies have reported an RP preceding speech production. For example, McAdam and Whitaker (1971) observed that it shows a small hemispheric asymmetry with the potential being maximal over Broca's area in the left hemisphere, an area known to play a major role in articulation. This negativity appeared up to 1 sec before articulation. However, there has been continuing controversy as to the cerebral versus extracerebral origin of this negativity. Szirtes and Vaughan (1977) conclude that the scalp recorded speech-related potentials either represent volume conducted activity from muscles involved in speech production or are heavily contaminated by such activity. In view of the continuing controversy over the validity of the speech-related negativity, this potential is not considered further in this review.

Sustained negativity. So far we have dealt with "slow" potentials elicited in paradigms with stimuli of a short duration. If the stimulus duration is prolonged, say, to 1 sec, a negative shift, called the sustained potential (SP), lasting for the whole duration of the stimulus, has been observed in addition to the onset and offset EPs (Keidel, 1971; Hillyard et al., 1978). SPs have been observed for stimuli in the auditory (Keidel, 1971; Jarvilehto and Fruhstorfer, 1973; Picton and Woods, 1975; Hillyard et al., 1978), visual (Keidel, 1971; Jarvilehto et al., in press) and somatosensory (Hillyard et al., 1978) modalities. The auditory SP was reported to have a maximum at the vertex and frontal locations, the focus being slightly more anterior than that of either the N1 or P2 components of the auditory EP and showing no reversal of polarity over the Sylvian fissure (Picton and Woods, 1975). The topography of the visual and somatosensory SPs has not been investigated in detail although Keidel (1971) found that the visual SP is larger over the occipital area than over the vertex and frontal sites.

The auditory SP exhibits an intensity function similar to that of the auditory N1-P2 component at the vertex. On the other hand, the auditory SP is much more resistant to decreasing ISI than the auditory N1 (Picton and Woods, 1975; Hillyard et al., 1978), and furthermore the recovery cycle of the SP shows little or no pitch specificity compared with the N1-P2 onset potentials (Hillyard et al., 1978).

It was suggested by Keidel (1971) that SP is an objective correlate of perception. This interpretation was regarded as having been contradicted by Jarvilehto and Fruhstorfer (1973) who showed that a break of 1 sec in a continuous tone elicits a negative shift very similar to the SP. It appears likely, however, that the shift observed by the authors was a CNV of a much larger amplitude than the SP caused by the continuous tone, and hence this result would not invalidate Keidel's interpretation. In fact, presently there is clear evidence that the SP is composed of two coincident negative potentials: (1) "true SP" (specific shift caused by the stimulus); (2) CNV. "True SP" (1) is supported by the findings that the SP occurrence is not dependent on the subject being given any particular task involving the stimuli (Jarvilehto and Fruhstorfer, 1973; Jarvilehto et al., in press) and that the auditory SP has been recorded during sleep (Picton and Woods, 1975). Moreover, the findings suggesting modality-specific topography reviewed in the foregoing lend credence to (1). CNV (2) is suggested by Picton and Wood's (1975) result that instructing subjects to detect an occasional tone of longer duration results in an increase in the SP amplitude. It is possible that this attentional enhancement of the SP is due to the superimposition of a CNV on the SP. However, the clearest evidence for separability of these two components comes

from Jarvilehto et al. (in press) in which the effect of repetition of the stimulus on SPs was studied. Auditory and visual stimuli of 1 sec duration were presented in trains of six stimuli with an ISI of 1 sec. Repetition rate was 1 train/min. The EEG was recorded from Cz, Pz and Oz. Both auditory and visual stimuli elicited SPs which during the first stimuli of the trains were maximal in amplitude at the vertex. Repetition of the stimulus in the stimulus train resulted in almost complete disappearance of the SPs. For auditory stimulation, a small negative shift remained only at Cz, whereas for visual stimulation a small SP was seen only at Pz and Oz. The authors suggested that the large component susceptible to habituation is associated with neural processes underlying orienting behavior, whereas the resistant component might reflect stimulus processing in the specific projection area.

Processing negativity. For some time it was generally accepted that (provided stimulus delivery rate is sufficiently fast) directing attention to one source of stimuli while ignoring other sources results in an increase in the amplitude of the N1 component of the EPs to stimuli from the attended source (Hillyard et al., 1973). This is the so-called N1 selective-attention effect. More recent evidence, however, indicates that the N1 effect is not the result of the enhancement of a true N1 component of the EP to attended stimuli but rather is due to a negative component of endogenous origin superimposed on the attended EP, a component which may only partly overlap the N1 component (Naatanen et al., 1978a,b). They observed a long-duration negative displacement of the EP to the attended ear stimuli in comparison to that to the unattended ear stimuli (randomized stimuli delivered at a regular ISI of 800 msec). The negative shift called 'processing negativity' began quite late at about 150 msec on the falling phase of the N1 component and continued for a further 500 msec. With a shorter ISI (250 msec) this shift began before the N1 peak (Naatanen et al., 1978c). Corroborating data were provided by Desmedt and Robertson (1977) who used a selective attention task to somatosensory stimuli randomly delivered to either hand at a mean ISI of 410 msec. EPs to attended stimuli exhibited a small negative shift with a mean onset latency of 78 msec, approximately 60 msec before the mean peak latency of the N1 component, which persisted in many cases beyond 200 msec poststimulus.

In their recent review, Naatanen and Michie (1978) have drawn attention to the fact that many of the early Hillyard findings should also be interpreted as due to the superimposition of a negative wave on the attended EP since the attention effects were often not entirely coincident in time with the N1 component. For example, in Schwent et al. (1976) the attended EP to central stimuli in their two single-cue conditions exhibits no clear N1 effect but does exhibit a negative displacement with an onset latency on

the falling phase of N1 giving the appearance of a filled P2.

Most experiments designed to study the effects of selective attention on EPs involve the presentation in random order of a number of different stimuli of brief duration, the stimuli differing on one or more cue dimensions. One of the stimuli is usually designated as a target on a given run, and the direction of attention is controlled by instructing the subject to count the number of occurrences of the target during the run or to make some response on detecting a target. One of the nontargets is usually more similar to the target than other nontargets because it shares a common cue characteristic with the target; for example, it may arise from the same spatial location as the target (the same ear as in Hillyard et al. (1973), or the same hand as in Desmedt and Robertson (1977)) or have the same pitch (as in the pitch-alone condition of Schwent et al. (1976)). It is usually assumed that subjects adopt the strategy of paying attention to the most target-like nontargets (stimuli in the attended source or channel) in order to be able to detect the (infrequently occurring) targets.

The earliest observed onset of the processing negativity is 60-70 msec (Hillyard et al., 1973; Desmedt and Robertson, 1977). Naatanen (1975) and Naatanen and Michie (1978) have argued that 60-70 msec is sufficient time for an easy discrimination between stimuli from different sources to be completed, and therefore the processing negativity is related to operations carried out after the decision relating to stimulus source has been made. What, then, determines the actual onset latency and duration of the processing negativity since an easy discrimination does not necessarily result in an early onset latency of the processing negativity? Naatanen and Michie have proposed that its onset latency and duration are determined by the difficulty of discriminating stimuli from the attended and unattended sources and the time pressure of the task which, in turn, is determined by the ISI structure and task requirements such as the difficulty of distinguishing targets from nontargets on the attended source. When an easy between-source discrimination is combined with a fast delivery rate, the processing negativity is early and of short duration and under these circumstances (Hillyard et al., 1973) can give rise to an apparent N1 facilitation. On the other hand, an easy discrimination combined with a slow delivery rate results in a prolonged-duration negativity with a considerably later onset as observed by Naatanen et al. (1978a,b). Thus it appears that while the onset of the negativity can begin early when the between-source discrimination is easy, it will only do so when the time pressure of the task requires that whatever processing associated with the negativity be completed early. On the other hand, when the discrimination between attended and unattended sources is more difficult, the onset latency of the processing negativity must of necessity be later as was observed for the central channel of the two single-cue conditions of the Schwent et al.

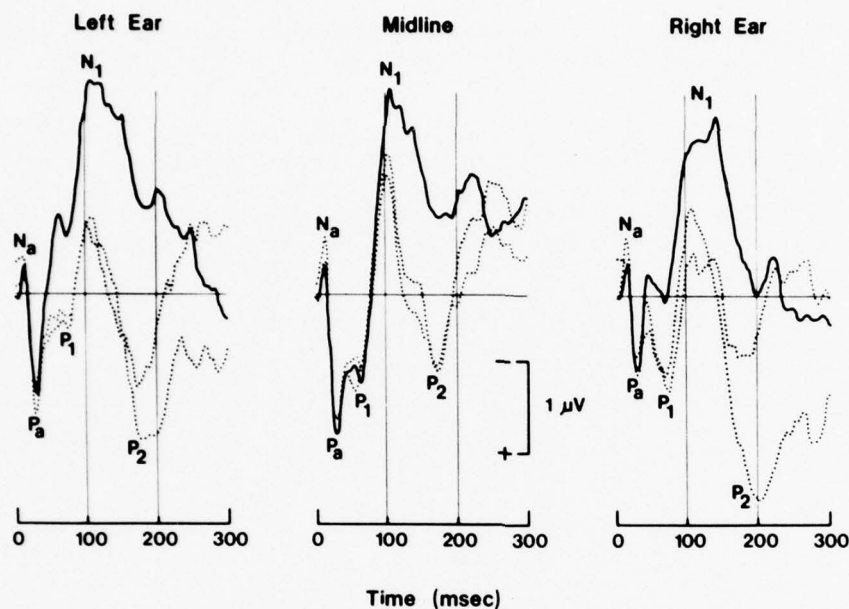


Fig. 1. Vertex EPs to left ear, midline (binaural) and right ear stimuli when attended (solid line) and when unattended (dotted lines). (From Van Voorhis et al., unpublished data.)

(1976) experiment. [See also the onset latency in Fig. 1 from an unpublished experiment conducted by Van Voorhis et al. (1976)].

Available evidence suggests that the processing negativity associated with attention to stimuli in the auditory modality has a frontal maximum (Naatanen et al., 1978c). A small amplitude negative displacement is also evident at T3 and T4 when referred to linked mastoids (Naatanen et al., 1978a,b). The processing negativity in the somatosensory modality is larger over contralateral parietal areas than the ipsilateral areas and smaller at central and frontal midline and lateral sites (Desmedt and Robertson, 1977). The topography of the processing negativity elicited by attention to stimuli in the visual modality has not been investigated in any detail although Van Voorhis and Hillyard (1977) have evidence that in some subjects an effect of selective attention at the N_1 latency can be produced at an occipital site (O2) when the stimulated visual field is contralateral to the scalp location but not when the stimulated visual field is ipsilateral. Much more investigation of the

scalp topography of the processing negativity is obviously required, but the available evidence is suggestive of a modality-specific topography.

Mismatch negativity. There is solid evidence for the existence of an endogenous negative component with a peak latency of approximately 200 msec (in the auditory modality) in response to a deviating stimulus (e.g., a click of a slightly stronger or weaker intensity than the other clicks) in a repetitive stimulus background (Squires et al., 1975; Snyder and Hillyard, 1976; Ford et al., 1976; Simson et al., 1977; Naatanen et al., 1978a,b,c). Stimulus deviation appears essential as infrequently presented single clicks did not evoke this component (Snyder and Hillyard, 1976). This component, called N2 or N200, or mismatch negativity, as Naatanen et al. call it, was elicited by a stimulus deviation whether attention was directed to the stimuli or not. Unlike the N1 and P2 components of the EP, it was very resistant to increased frequency of the background stimuli (Snyder and Hillyard, 1976). N2, or mismatch negativity, often had a short, EP component-like waveform which could be easily observed as the "N2 component" in the EP to the deviating stimuli. On the other hand, Simson et al. (1977) and Naatanen et al. (1978a,b) revealed the mismatch negativity by subtracting the EP to background stimuli from that to the deviating stimuli. The latter authors observed it to last for at least 200 msec. In many studies (e.g., Squires et al., 1975; Snyder and Hillyard, 1976), the mismatch negativity was followed by P3a, a frontally dominated late positivity (with somewhat shorter latency than the parietal P3), and they were often regarded as intimately linked ("N2-P3a complex"). It was, however, demonstrated by Naatanen et al. (1978b) that under dichotic listening conditions the mismatch negativity with no later positivity is elicited by a deviating input among repetitive background stimuli to the unattended ear (while in the attended ear this positivity was observed).

A fronto-central topography of the (auditory) mismatch negativity was generally observed in these studies. Naatanen et al. (1978b) found that there was another focus near the specific sensory areas of audition, as the amplitudes from the T3 and T4 sites were even larger than those from the vertex. Clear data lending credence to the modality-specific distribution of the auditory mismatch negativity were presented by Simson et al. (1977) who also showed a similar effect within the visual modality. In contrast to the auditory modality, frontal activity did not contribute appreciably to the visual mismatch negativity.

Detection negativity. In Cooper et al.'s (1977) study on vigilance of operators watching a visual display for a long time, a videotape recording was made by televising a model landscape across which correctly scaled vehicles moved singly at infrequent, unpredictable times. Vehicles entered along any of the four roads

from the left or right or from behind clumps of trees in the middle of the picture. The observer was instructed to press a switch whenever a vehicle appeared in the display. The mean detection time was 4.3 sec. About 1 sec before the switch was pressed to indicate detection, the gaze transferred to the region of the vehicle, and detailed scanning of this part of the display began. During this scanning a large centro-parietal positive shift was reported to occur. (This potential was not directly related in time to the eye movements or to the switch press.) Interestingly, this positivity was often preceded by a slow centro-parietal negative shift which could start while the eyes were scanning other parts of the display. According to the authors, it presumably starts when something seen in peripheral vision directs the eye scan towards the area of the display containing the vehicle. This negativity was reported to be similar in form to the CNV and was suggested to indicate preparation for action. (It is uncertain to what extent this negativity is an RP preceding the fixation of the gaze to the target).

Missing-stimulus negativity. It has now been well established that the nondelivery of an expected stimulus gives rise to an "emitted" potential, the missing-stimulus potential, which consists of a long latency positive component which is preceded by a negative component (Klinke et al., 1968; Ford et al., 1976; Simson et al., 1976). The late positive component of the missing-stimulus potential appears to be identical to the P300 component elicited by stimuli which deliver task-relevant information as shown by their similar scalp distributions (Simson et al., 1977) and by the fact that they respond similarly to changes in event probability (Ruchkin et al., 1975). The negative component of the missing-stimulus potential, henceforth called the 'missing-stimulus negativity' (MSN), has been most successfully elicited by paradigms in which a stimulus omission occurs in a regular train of stimuli. Under these circumstances the MSN appears to begin at the point in time at which the missing stimulus would have occurred (Simson et al., 1976; Ford et al., 1976).

The MSN has been observed for omission of stimuli in the visual (Simson et al., 1976), auditory (Simson et al., 1976; Ford et al., 1976) and somatosensory modalities (Klinke et al., 1968). Simson et al. (1976) have shown that the scalp topography of the MSN is modality-specific in the visual and auditory modalities. The visual MSN shows a pre-occipital maximum and, in many cases, a secondary focus at the vertex. The topography of the visual MSN is, in fact, quite similar to the scalp topography of the P2 (and to a lesser extent N1) component of the visual EP, suggesting that they arise from similar cortical regions, probably visual areas 18-19 for the posterior focus and the frontal premotor cortex for the central focus. The auditory MSN, on the other hand, has a posterior frontal maximum which appears to extend laterally toward the posterior superior temporal region. Simson et al. (1976) have suggested that

the auditory MSN arises from activity in the cortex of the supra-temporal plane which is projected to the surface of the central region and a field overlying the auditory association cortex on the lateral surface of the superior temporal gyrus. The scalp topography of the somatosensory MSN has not yet been investigated.

Further modality differences in the MSN are evident from modality effects on the MSN peak latency. In the paradigm used by Simson et al. (1976) (involving the omission of a stimulus in a train of stimuli occurring regularly at a rate of 1/sec) the visual MSN peaked at a mean latency of 275 msec while the auditory MSN peaked at 230 msec. The peak latency of the MSN also appears to be affected by ISI as Picton et al. (1974) found that progressive increases in the ISI of the train of stimuli produced MSNs of longer latency and smaller amplitude. The smaller amplitude of the averaged MSN with increasing ISI could well be in part due to greater variability of the MSN latency over single trials. Both effects presumably reflect the longer, more variable and flatter time course of expectancy observed when the ISI is prolonged (Naatanen and Merisalo, 1977).

The occurrence of the missing-stimulus potentials is not dependent on the subject being given any particular task relating to the missing stimuli since the negative-positive complex can be recorded when the subject is instructed to "keep as alert as possible and to direct attention to the stimuli" (Klinke et al., 1968) or when the subject is instructed to ignore the stimuli and read a book (Ford et al., 1976). Instructions to attend to the missing stimuli and to push a button as quickly as possible on detecting a stimulus omission does not affect the amplitude of the MSN recorded at the vertex but does increase its latency (Ford et al., 1976). Possible changes in the scalp topography of the MSN with attention have not been investigated.

CONCLUSION

The above review appears to suggest that the negative shifts classified on the basis of eliciting situation or performance are composed of one or several of the following components:

- 1) Frontal nonspecific negative shift. This is a fronto-central negative shift reaching its peak some 500-700 msec from the stimulus onset observed most clearly when an auditory stimulus is used. In an S1-S2 paradigm, it can exist even without S2. Its amplitude reflects the intensity and significance of the stimulus, and its time course appears to be independent of ISI. There is much evidence for its being associated with some subcortical nonspecific activation processes. This negative shift is often associated with a slow positive shift maximal over the parietal area.

2) Central, nonspecific widely distributed negative shift.

Called the "true CNV" in the foregoing, this is S2-related in S1-S2 paradigms and is very sensitive to ISI and task demands but can also exist outside or independently of the S1-S2 paradigm. It was suggested to reflect the degree of activation of the subcortical nonspecific activation mechanisms mainly reflecting the nature of the task and task demands in performance situations. This view appears to clarify two persistent issues in the field:

(a) The generally low correlations between the amplitude of CNV and performance: if CNV mainly reflects the degree of increased activity in some nonspecific activation centers rather than some more specific factors in performance and preparation for it (e.g., expectancy or attention), the low correlations between various "activation measures" (varying within the relatively narrow limits of the test situation) and performance (see Naatanen, 1973);

(b) Reaction time and other motor tasks as optimal conditions for CNV elicitation: there is plenty of evidence for large physiological changes regarded as indicating "activation" increase during the S1-S2 interval of the reaction time paradigm. On the other hand, for example a sensory discrimination task is performed by the organism with much less extensive mechanisms which would explain why no large ERPs are generated. Moreover, in sensory tasks there is emphasis on accuracy (rather than speed of performance) for which a calm, relaxed attitude might be ideal.

3) Modality-specific negativity. The reviewed evidence points to the conclusion that various performances with a sensory aspect are associated with a modality-specific negative shift. There seem to exist three types of such shifts. The first is associated with template mismatch (missing stimulus negativity appears to be a mismatch negativity too) underlying automatic passive-attention and may play a role in the initiation of the orienting response. The second type is processing negativity, that associated with voluntary attention to and further processing of certain stimuli selected in preliminary processing. (Many other types of tasks probably induce such shifts as well.) Detection negativity probably is one form of processing negativity; it is associated with intensive processing on detection of a preliminary cue for a target. As to the differences between the mismatch and processing negativities, the former appears to be of relatively larger size over the sensory-specific areas and has a ramp-like, short waveform while the latter often is a steady, long-duration shift. (Both have a quite strong nonspecific component. This might be intimately interlinked with the specific process to the degree that they cannot be disassociated. In such a case it would be appropriate to deal with the mismatch negativity and the processing negativity as if each were composed of one component. Generally the division into different components is based on the idea that the latter are

experimentally separable in that they show different relations to some experimental manipulations. (For an elegant example, see the Jarvilehto et al. experiment reviewed above.) The third type is suggested to be the specific component of the sustained potential.

4) Motor-specific negativity. Topographical data showing hemispheric asymmetries contralateral to the responding limb suggest that in tasks with a motor performance there also exists a motor-specific slow negative shift.

5) Some other forms of function-specific negativities. Examples include those associated with word and pattern processing.

The traditional CNV was suggested to be composed of several of these components. Perhaps they all are present when an auditory S1 (producing the frontal negativity) is used in a reaction time task with word stimulus. The RP was regarded as being composed of motor-specific negativity and the central type of nonspecific negativity. (There is evidence for a lack of frontal negativity, even for frontal positivity, during the RP). On the other hand, the S1-related slow negativity known as the orienting component of the CNV appears the same as component 1), but it is possible that there are modality-specific aspects in its topography too. The remaining five negativity shifts classified on the basis of situation or performance (speech-related negativity is omitted here), sustained negativity, processing negativity, mismatch negativity, detection negativity and missing-stimulus negativity, all appear to be composed of a nonspecific (either frontal or central type) and a modality-specific component.

Of these five, mismatch and missing-stimulus negativities appear to be closely related as stated above, and their topography is similar. They both seem to represent an automatic type of detection of, or response to, an environmental change. Sustained negativity (its sensory-specific component) also appears to be a relatively inflexible, automatic type of negativity, depending to a great extent on physical stimulus characteristics. The nonspecific central negativity, motor-specific slow negativity, processing negativity and detection negativity, on the other hand, appear to be of voluntary or flexible character, reflecting to a great degree higher cognitive functions. For example, processing negativity seems to be elicited by the stimulus the subject is instructed to pay attention to. As discussed above, detection negativity might be one form of processing negativity. The suggested components of negative shifts as classified into two main categories are presented in Table I. In light of the available evidence the nonspecific frontal component appears as a borderline case between the negative shifts associated with "first-order" and "higher-order" processes.

Table 1. Suggested components of negative shifts.

-NONCOGNITIVE	-COGNITIVE
-INFLEXIBLE	-FLEXIBLE
(not much effect of variables such as learning, stimulus significance, attention, task, etc.)	(effect of variables such as learning, stimulus significance, attention, task, etc.)
-DETERMINED BY PHYSICAL STIMULUS FEATURES	-NOT DETERMINED BY PHYSICAL STIMULUS FEATURES
-"FIRST ORDER"	-"HIGHER ORDER"
SUSTAINED POTENTIAL (specific)	NONSPECIFIC CENTRAL ("true CNV")
MISMATCH NEGATIVITY	RP (specific)
	PROCESSING NEGATIVITY
NONSPECIFIC FRONTAL	

SUMMARY

As research in the neurophysiology of higher cerebral functions progresses, more and more different types of brain potentials in performance situations are discovered. The recent years have especially brought up candidates for new variants of endogenous negative potentials. It appears that besides the CNV we have at least the following negative shifts: Bereitschaftspotential; "orienting component" of the CNV; speech-related negativity; sustained negativity; processing negativity; mismatch negativity; detection negativity; missing-stimulus negativity. The present paper attempts to systematize these more or less overlapping negative shifts which have mainly been named on the basis of situation or performance eliciting them. Especially the lack of detailed knowledge of the scalp topography of most of these negative shifts in different situations makes it difficult at the present stage of research to determine their mutual relationships.

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EVENT RELATED POTENTIALS IN LANGUAGE AND NON-LANGUAGE TASKS IN
PATIENTS WITH ALEXIA WITHOUT AGRAPHIA

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The concurrent study of behavior and event related potentials (ERPs) from different scalp locations can provide converging evidence for the brain structures and functions which underlie normal human cognitive processes. The study of behavior and ERPs in patients with localized brain damage that has resulted in specific behavioral deficits can, in theory, complement studies of normal subjects by: (1) describing changes in particular aspects of ERPs associated with disturbances in particular cognitive functions, and (2) permitting correlations between the absence or distortion of particular ERP components and damage to particular areas of the brain. Results from studies like these may provide information as to those aspects of cognitive functions that are reflected in particular ERP components and may also provide information as to the neural origins of different ERP components.

We and others have looked for evidence of cerebral specialization of function in ERPs recorded from the two hemispheres of normal adults. Cerebral specialization of function refers to the fact that the left and right cerebral hemispheres of man do not contribute equally to certain specific cognitive abilities. In most normal adults the integrity of the left cerebral hemisphere is more important for language functioning, and the integrity of the right hemisphere is more important for the performance of certain non-language perceptual tasks. Evidence for this differential functional specialization comes from studies showing greater deficits in language functioning following damage to the left hemisphere than damage to the right hemisphere, but greater deficits in perceptual functioning such as the recognition of faces and orientation in space after damage to the right than to the left

cerebral hemisphere (Luria and Karasseva, 1968; Teuber, 1974). Studies of normal adults, showing better perception and recall of language material presented to the right ear and right visual field (which project more directly to the left hemisphere) and better perception and recall of certain non-language material presented to the left ear and left visual field (which project more directly to the right hemisphere), reveal similar differential specializations of the two hemispheres in the intact brain (Kimura, 1967; Klein et al., 1976; Knox and Kimura, 1968). Over the last decade a number of studies have reported left/right differences in the ERP which are thought to reflect functional hemispheric asymmetries (Wood et al., 1971; Brown et al., 1976). Many would agree, however, that the asymmetries reported have been elusive and, when obtained, less prominent than one might expect from the neuropsychological studies of cerebral specialization. Many of these studies have methodological shortcomings which make interpretation of the results difficult (see the reviews of this literature by Friedman et al., 1975; Galambos et al., 1975; Donchin et al., 1977). Perhaps the primary shortcomings of many of these studies are the lack of real language stimuli (for example, many investigators employ meaningless syllables such as /ba/, /da/) and the failure to engage the subject in a demanding task which requires language processing.

We investigated the possibility that stronger ERP asymmetries indicative of cerebral specialization might be obtained if we recorded ERPs in tasks which produce marked behavioral asymmetries (Neville et al., 1977). This type of design, in addition to engaging the subject in a demanding task, also has the advantage of providing converging behavioral evidence for a functional interpretation of any ERP asymmetries obtained. We found that ERPs (N1) to auditory and visual language stimuli were significantly larger from the left than the right hemisphere when subjects performed tasks which resulted in a lateral behavioral asymmetry. The most difficult task, the simultaneous presentation of two different words to the two visual fields, produced the most marked behavioral and ERP asymmetries: in every subject who correctly reported more words from the right than the left visual field, the N1 from the left hemisphere was larger than that of the right hemisphere. Thus, the functional specialization of the left hemisphere for language processing is reflected in ERPs recorded from subjects engaged in demanding tasks which result in behavioral asymmetries.

In the present investigation we employed paradigms similar to those described above in the study of three patients with the syndrome known as alexia without agraphia (Ajax et al., 1977; Vincent et al., 1977). This disorder is of considerable interest to the neuropsychologist because it is a striking example of how a discrete structural lesion can selectively dissociate one particular

aspect of language (reading) from language functioning as a whole. In these patients the ability to read is severely disrupted. This occurs without impairment of the ability to write. These patients can write normally, spontaneously or to dictation, but later cannot read what they have just written. The patients may be able to read individual numbers and letters and some simple words, although slowly and laboriously. Speech and the comprehension of speech are normal in these patients as is the ability to name visually presented objects.

This rare syndrome was described by Wernicke (1885), who proposed that it might be due to a lesion which spared the angular gyrus (the 'storehouse for visual words'), thereby preserving the ability to write, but destroyed the pathways whereby visual information reaches this center and is decoded. Dejerine's (1892) description of the brain of such a patient who came to autopsy confirmed Wernicke's hypothesis exactly. Dejerine's patient had suffered an infarct of the left occipital lobe (thereby rendering him blind in the right visual field) and the splenium of the corpus callosum (thereby preventing the transfer of visual information from the left visual field and intact right occipital cortex to the left angular gyrus). The preserved left angular gyrus presumably enabled the patient to write.

This 'disconnection' model of the functions of the brain underlying the ability to read continues to receive support (Geschwind, 1965). While this theory can often predict the site of a lesion on the basis of initial behavioral deficits, there is little understanding of the possible mechanisms involved in the improvement of function which some patients show. Often in this syndrome the reading deficit is not absolute immediately after the injury and patients may show some improvement in the ability to read months and years after the initial trauma. Several explanations for this improvement are possible. Conceivably, for example, some recovery of function might occur if the right angular gyrus somehow is able to assume certain functions that the left angular gyrus normally performs. Alternatively, perhaps over time visual language information presented to the left visual field could cross over to the left angular gyrus by portions of the corpus callosum anterior to the splenium. In the present investigation we recorded ERPs to visually presented language and non-language stimuli from left and right, central, parietal and occipital electrode sites to determine whether the distribution and/or form of the ERP might differ in these patients in a systematic way from normal.

METHODS

Subjects

Our subjects were three men with the syndrome of alexia without agraphia and three normal controls matched for sex, visual acuity, age and handedness.

Patient 1. PW was a 28 year old, right-handed male. Eight years prior to testing he suffered a penetrating head trauma which destroyed the left occipital cortex and splenium of the corpus callosum [as seen on computerized axial tomography (CAT) scan]. Immediately following his injury PW had a dense right hemianopsia and was severely impaired in his ability to read single numbers, letters or words. He was never impaired in his ability to write, to name visually presented objects, to speak or to understand speech. This patient has shown considerable recovery in the 8 years since the injury and can now read single numbers, letters and some three- and four-letter words.

Patient 2. CP was a 60 year old, right-handed male who, 9 months prior to testing, suffered an occlusion of the left posterior cerebral artery (as seen by cerebral angiography) which compromised the left occipital lobe and splenium of the corpus callosum. Immediately following the occlusion he had a dense right hemianopsia and made many errors in reading single letters and words. He experienced no difficulty in writing, speaking or understanding speech.

Patient 3. BR was a 60 year old, left-handed male who, 1.5 months prior to testing, underwent surgery for the removal of a tumor involving the left occipital lobe and splenium of the corpus callosum (CAT scan). Following surgery he had a dense right hemianopsia, had some difficulty reading single numbers and letters and had a severe deficit in reading words. His abilities to write, to speak and to understand speech were not impaired.

At the time of testing the patients were out of the hospital and were functioning quite normally. The major obstacle each patient had to adjust to was his right hemianopsia and the difficulty reading. All patients have shown some recovery in the ability to read since their initial insult. In fact, the youngest patient (PW) now reads at a third grade level.

Stimuli

We recorded visual ERPs to full field white and colored flashes and to unilateral squares of white light, numbers, letters, three-

and four-letter words and line drawings of common objects. Here we report only the methods and results for full field white flashes, four-letter words and line drawings.

All visual stimuli consisted of slides back-projected onto a translucent screen. The edges of all slides coincided precisely with the edges of the screen to yield a rectangular field 13° wide and 8.5° high. Subjects saw 1.25 meters from the screen and fixated a red spot which was always at the center of the field. Stimuli were tachistoscopically presented for 100 milliseconds (msec). Except for the full field flashes, all stimuli were white patterns (words and line drawings) on a black background. They were presented so that their nearest edge began 2° to the left or right of the fixation point. All stimuli were presented at irregular interstimulus intervals ranging from one to four seconds.

1. Flashes of white light. These covered the full field and were 690 candelas/meter² (cd/m²). Subjects simply viewed the screen with no assigned task.
2. Four-letter words. Eighty-five different four-letter words were randomly presented once to the left and once to the right visual field. Each word was 2.5° in length. The brightness of these stimuli was 200 cd/m². The subject's task was to verbally report the word after each trial.
3. Line drawings. Thirty different line drawings of common objects (e.g., shoe, train) were presented randomly to the left and right visual fields. These stimuli were 2.5° in length and 2° high. There were on average 170 cd/m². After each trial subjects reported the name of the object presented in the slide.

Procedure

During all stimulus presentations the EEG was recorded from electrodes placed at O1 and O2, P3 and P4, C3 and C4 (International 10-20 system) and from beneath the right eye, all referred to the linked mastoids. Electrode impedances were all below 3000 ohms. Signals were amplified with Grass 7P5 amplifiers (TC = .45 seconds) and were recorded on an FM tape recorder (Vetter model A) for off-line computer analysis.

Each control subject was tested on all stimuli in one four-hour session. Each patient was tested twice on all stimuli in two different four-hour sessions. Stimuli were presented in blocks according to stimulus type. During all tasks an experimenter sat next to the subject and pointed to the fixation spot prior to each trial, monitored the subject's eye movements to ensure central fixation,

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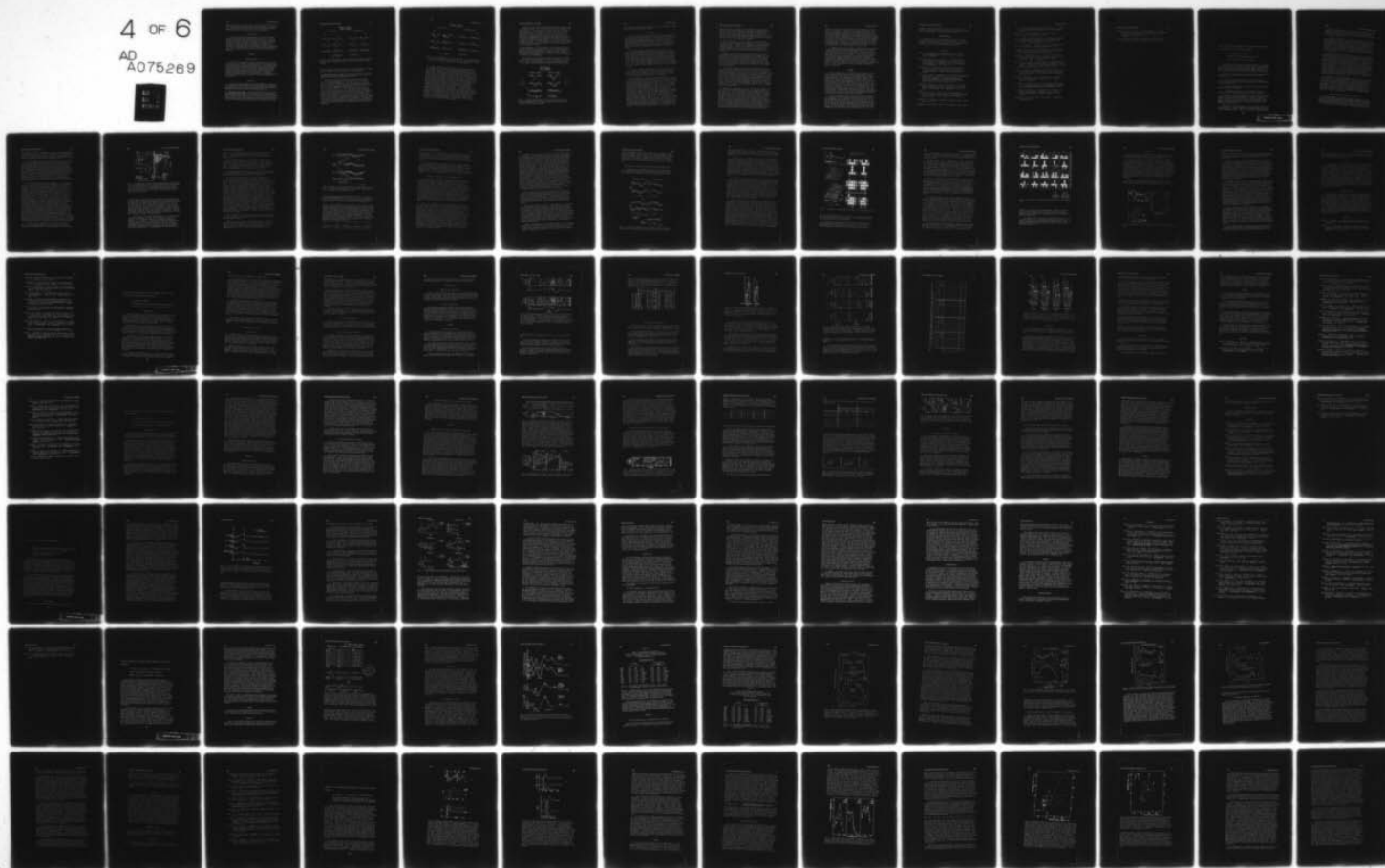
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indicated (about 1 sec after stimulus presentation) when the subject could respond and recorded his verbal response. All subjects wore earphones through which white noise was presented to mask sounds produced in conjunction with stimulus delivery.

Data Analysis

The EEG was digitized and averaged on a PDP 11/45 computer employing programs which automatically rejected trials on which excessive muscle artifact and eye movements occurred. ERPs were averaged separately according to stimulus type and according to whether the subject responded correctly or incorrectly. We measured the peak amplitude of ERP components N1 and P3 relative to an average prestimulus baseline of 100 msec. We also measured the area of the positivity between 200 and 300 msec relative to the baseline.

RESULTS

Behavioral Data

On average, the controls accurately reported 67% of the four-letter words. All patients responded "nothing" to all right visual field presentations of words (confirming their right hemianopsia). Patient PW correctly reported 60% of left visual presentations of four-letter words. Patient CP accurately reported 24% of left visual field presentations of four-letter words, and patient BR accurately reported 30% of four-letter words. All subjects performed virtually perfectly in reporting the line drawings except that the patients reported "nothing" to all right visual field presentations.

ERP Data

In general, the morphology of the ERP waveform in control subjects showed a prominent negativity around 180 msec post-stimulus presentation (N1) and (except in the passive flash run) a positivity maximal around 350 msec post-stimulus presentation (P3).

1. Flashes of white light. In control subjects these (full field) stimuli evoked an N1 around 150 msec after stimulus presentation. These responses were present at both left and right hemisphere leads. In the patients (for whom this was a unilateral, left visual field stimulus due to their right hemianopsia) the flash did not evoke an N1 at the left hemisphere electrode sites but evoked an N1 of com-

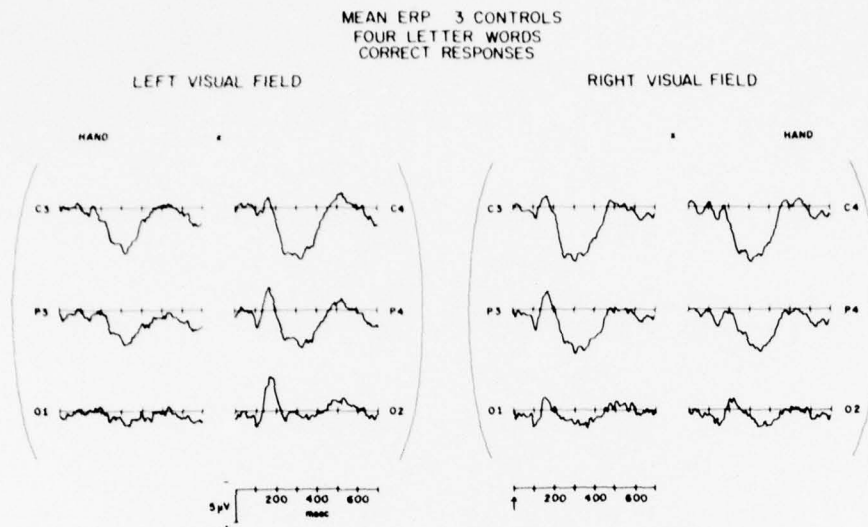


Fig. 1. ERPs averaged over control subjects to correctly reported presentations of four-letter words to the left and right visual fields.

parable amplitude to the controls at the right hemisphere electrode sites. In this (no task) situation, no P3 was elicited.

2. Four-letter words. Figure 1 shows ERPs averaged over the three control subjects to presentations of four-letter words (correctly reported) to the left and right visual fields.

Left visual field presentations produced an N1 (170 msec) over the right hemisphere at O2 (5.8 μ V), P4 (3.9 μ V) and C4 (2.3 μ V); at the left hemisphere sites N1, if present, was very small. In contrast, right visual field presentations produced a large N1 at left hemisphere electrode sites (O1 3.6 μ V; P3 3.7 μ V; C3 3.7 μ V) and a small N1 at right hemisphere electrode sites (O2 2.1 μ V; P4 0.4 μ V; C4 1.3 μ V). The ERPs to left and right visual field presentations of words also contained a P3 (maximal about 325 msec after word onset) at central (on average, 10.5 μ V) and at parietal leads (8.6 μ V), but not at the occipital leads. This P3, in contrast to the asymmetrical N1, was of equal amplitude at the left and right hemispheres, and its amplitude was not altered as a function of left or right field presentation. A comparison of the ERPs to four-letter words reported correctly and incorrectly revealed no striking differences in morphology or left/right distribution.

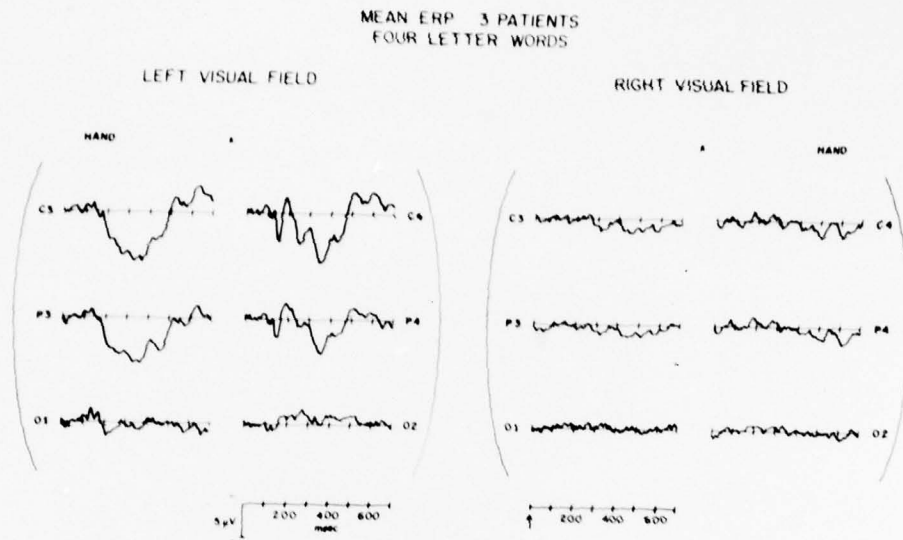


Fig. 2. ERPs averaged over the three patients to correctly reported presentations of four-letter words to the left visual field and ERPs to right visual field presentations of the same stimuli.

Figure 2 shows ERPs averaged over the three patients to correctly reported presentations of four-letter words to the left visual field, and ERPs to right visual field presentations of the same stimuli. Presentations of these stimuli to the right (hemianopic) visual field produced no discernible ERP components. Correctly reported four-letter words presented to the (preserved) left visual field did not produce an N1 over the lesion (O1), and also failed to evoke an N1 over the intact right occipital cortex (O2). More anteriorly, the N1 was present at right parietal (mean 2.5 μ V) and at right central (mean 2.2 μ V) leads. Left visual field presentations of four-letter words also produced a P3, maximal around 350 msec post-stimulus presentation, at central (mean 9.0 μ V) and parietal (mean 7.5 μ V) leads. In contrast to the symmetrical positivity in control subjects, the amplitude of this positivity was asymmetrical in patients, especially at the parietal leads: it was broader and larger at left (mean area between 200 and 500 msec in arbitrary units = 70) than at right (mean area 200 - 500 msec = 30) hemisphere leads. There were no consistent differences in morphology, amplitude or distribution between ERPs to left visual field presentations of four-letter words reported correctly and incorrectly by the patients.

Figure 3 presents the left visual field data of Figures 1 and 2 in a different way. ERPs from the left and right hemispheres are superimposed. In controls the N1 is larger from the right hemisphere than the left hemisphere, while the P3 response is essentially symmetrical. In patients, the N1 is absent at all left hemisphere sites and over the right occipital lead, but has an essentially normal appearance at right central and parietal leads. Note also the asymmetrical (left greater than right) positivity (shaded area) between 200 and 500 msec which is most pronounced at the parietal leads. This ERP asymmetry to correctly and incorrectly reported words was consistently present in all three patients during both recording sessions.

3. Line drawings. In control subjects left visual field presentations of line drawings evoked an N1 at occipital and parietal leads which closely resembled the responses to words (asymmetrical, right hemisphere larger than left). Similarly, left visual presentations of line drawings also elicited a P3 which was symmetrical at left and right hemispheres.

In contrast to the results for words, the patients' responses to left visual field presentations of the line drawings contained an N1 at right occipital (mean 4.1 μ V) and right parietal (mean 3.5 μ V) leads. As with words, ERPs from the left hemisphere did

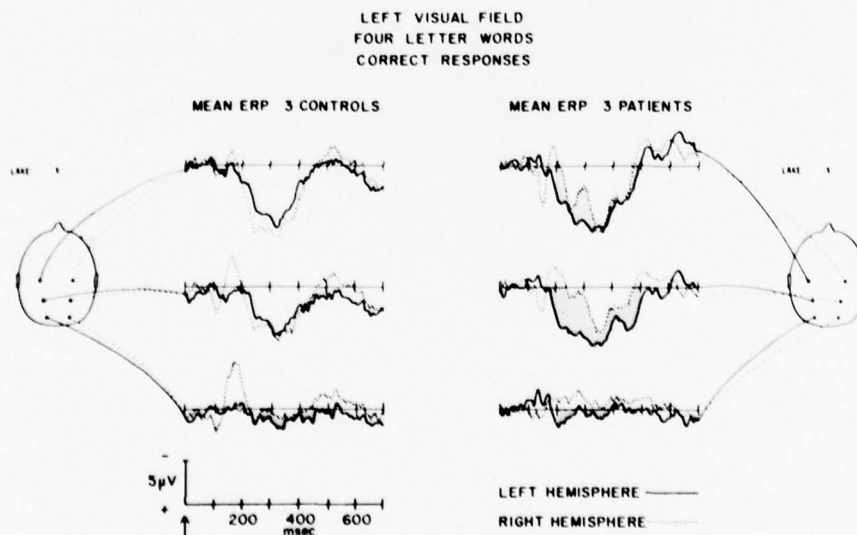


Fig. 3. Controls' and patients' ERPs from left and right hemispheres (superimposed) to correctly reported left visual field presentations of four-letter words.

not contain an N1, and these stimuli elicited a P3 which was larger from left than right parietal leads.

DISCUSSION

In general, all left visual field and full field stimuli produced ERPs of similar morphology for control subjects and patients. The waveform was characterized by an N1 (about 180 msec after stimulus presentation) and, when subjects performed a task, a P3 (maximal around 350 msec after stimulus onset). Differences between control subjects and patients were found in the anterior/posterior and left/right amplitude distributions of these components.

In control subjects the lateralized presentation (to the left or right visual field) of words and line drawings produced ERPs in which the N1 was larger over the hemisphere contralateral to the field of stimulation, and small or absent over the ipsilateral hemisphere. This result is an agreement with what might be expected on the basis of the anatomy of the visual pathways if the N1 is generated in the hemisphere of the primary receiving area. Other investigators (Nakamura and Biersdorf, 1971; Shagass et al., 1976) have reported similar results. Here the N1 asymmetry, seen over occipital cortex, extended to parietal and central leads as well.

In patients, stimuli presented to the right visual field were not perceived, and they did not evoke any discernible ERP components. This result suggests that the N1 and later components were generated at or beyond the level of the primary receiving areas in the hemisphere contralateral to stimulation.

In these patients, correctly reported presentations of words to the left visual field did not produce an N1 over the left hemisphere or over the intact right occipital cortex, but did evoke an N1 at right hemisphere parietal and central sites. Other studies of hemianopic patients (Wildberger et al., 1976) report normal ERPs over the intact hemisphere to stimulation of the preserved visual field. The different results found here might be a consequence of the fact that our patients, in addition to having left occipital damage, have also sustained damage to the splenium of the corpus callosum. Perhaps the additional damage to the callosal fibers joining the two occipital lobes disrupted the functioning of the right occipital lobe. This hypothetical right occipital damage, however, did not affect the visual acuity of the patients, nor did it affect the N1 at right parietal and central electrode sites. Moreover, the suggestion that secondary right occipital damage disrupted the occipital N1 is complicated by the fact that left visual field presentations of line drawings did produce an N1 over right occipital cortex in the patients. The

different results for words and line drawings suggest that the nature of the evoking stimuli may determine the distribution of the N1 in patients such as these. The anterior distribution of the N1 over the right hemisphere for words, but not for line drawings, may indicate that visual language information is relayed to those areas of the right hemisphere where transfer across intact portions of the corpus callosum is possible.

This interpretation of the N1 results is weakened by the dissimilarities in the physical characteristics of the words and the line drawings. Although their average spatial luminance was comparable (words 200 cd/m²; line drawings 170 cd/m²), other optical parameters such as contour density and complexity are virtually impossible to equate across these two categories of stimuli.

Further tests of these and other patients may aid in the interpretation of the results found for N1. For example, if the absence of the splenium is the important factor in the anterior distribution for words, patients with an infarct of the splenium (but intact left occiput) should show the same results as these patients. Patients with left occipital lesions which have spared the splenium should show a normal N1 distribution to left visual field presentations.

All subjects verbally reported the laterally presented words and line drawings, and when they did so their ERPs contained a P3 at parietal and central leads. In controls this P3 was symmetrical over the two hemispheres independent of field of presentation. This dissociation between the distribution and symmetry of N1 and P3 supports current opinion which views these two ERP components as distinct, both in terms of their functional significance and in terms of their neural origins (Hillyard and Picton, in press). This symmetry of the P3 to unilateral stimulation might be attributed to complete transfer across interhemispheric commissures of a response generated in one hemisphere or to generation of the P3 by a midline subcortical structure(s).

Whereas the P3 amplitude in control subjects was symmetrical over the left and right hemispheres, it was asymmetrical in all three patients. The P3 at parietal leads was consistently broader and larger from the left than from the right hemisphere. Although the precise nature of the psychological variables which determine the amplitude of the P3 are poorly understood, it has been interpreted as a sign of the later stages of information processing including response set selection, decision making and the reduction of uncertainty (e.g. Hillyard and Picton, in press; Sutton et al., 1967). The parietal leads from which we recorded roughly underlie the left and right angular gyri. One might have expected, if patients were able to use the right but not the left angular gyrus in reading words presented to the left visual field, that a P3

would be elicited which was larger over right than left parietal areas. No evidence in support of this notion was found in the present investigation. Moreover, the asymmetry was found in ERPs to all task relevant stimuli. This suggests that perhaps the structural damage to the adjacent left occipital lobe was responsible for the larger P3 amplitude over the left parietal area; perhaps the larger P3 resulted from increased excitability at left parietal cortex resulting from loss of inhibition from the adjacent damaged occipital cortex. Similar tests of patients with left occipital lobe damage which has spared the splenium (and who have no reading deficit) may aid in the interpretation of this result.

To summarize, the major findings reported here are the absence, in patients with alexia without agraphia, of an N1 over intact right occipital cortex to correctly reported words presented to the left visual field and the asymmetrical (left larger than right) amplitude of the P3 in these patients. These results, although clear and consistent, are difficult to interpret from the point of view of the proposed mechanisms underlying the syndrome of alexia without agraphia and also from the point of view of current knowledge of the functional and structural correlates of the N1 and P3. Additional studies on these and similar patient populations may aid in the clarification of the neural bases of cognitive processes and ERPs.

SUMMARY

We have simultaneously studied ERPs and performance on language and non-language tasks in normal control subjects and in three patients with the disconnection syndrome known as alexia without agraphia. This syndrome, in which every aspect of language functioning was intact except the ability to read, was produced by a lesion which compromised left occipital cortex and the splenium of the corpus callosum (as seen on CAT scan). We recorded ERPs from left and right central, parietal and occipital leads and from the eyes, all referred to linked mastoids. The stimuli were numbers, letters, three- and four-letter words and line drawings of common objects presented to the left and right visual fields. ERPs from left and right hemispheres were averaged separately according to stimulus type, visual field and whether or not subjects accurately perceived the stimuli.

Both the left/right and the anterior/posterior distributions of the patients' ERPs differed from those of control subjects. Most remarkable was the absence, in all three patients, of the N1 response over the intact right occipital lobe, even when patients accurately read words presented to the (good) left visual field. The N1 was present more anteriorly over right parietal and central sites, however. The other major result was a large asymmetry (left parietal greater than right parietal) in the P3

response of all three patients (but not in controls). These results are tentatively discussed in terms of possible functional and structural changes in alexia without agraphia.

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SPATIAL AND TEMPORAL DISTRIBUTION OF OLFACTORY EVOKED POTENTIALS
AND TECHNIQUES INVOLVED IN THEIR MEASUREMENT

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Finkenzeller (1966) and Allison and Goff (1967), in studying the olfactory system, succeeded in finding olfactory evoked potentials (OEPs) on the intact skull of awake humans. Partly due to the technical difficulties associated with olfactory stimulation, however, there has been little subsequent progress in this area.

In order to properly record and analyze OEPs from awake humans and relate them to the underlying olfactory processes it is necessary to:

1. Use an olfactory stimulus with precisely determined intensive and temporal characteristics (including an instantaneous onset and offset time);
2. Eliminate (or minimize) the artifactual components that distort or mask the OEPs; and
3. Present many repetitions of the stimulus in order to improve the signal-to-noise ratio of the recorded potentials.

In regards to the first requirement, several serious technical problems have made it quite difficult in the past to produce an exactly reproducible olfactory stimulus. The first part of this paper includes the description of a new stimulating device that enables us to produce, as often as desirable, a stimulus with constant characteristics.

Satisfying the second requirement cited above has proven to be equally difficult. Several sources of artifactual intrusions have been described previously. Some of them include (listed according

to increasing difficulty): thermoreceptive disturbances, auditory responses, synchronization of the potentials with respiration, somatosensory (tactile) responses, eye blinking and somatosensory responses by chemical stimulation of free trigeminal nerve endings by the odorous substances.

The latter two sources of artifactual disturbances have been particularly bothersome. Eye-blinking is a disturbance well known to investigators of EEG phenomena in other sensory modalities. Chemical stimuli, however, are even more prone to elicit eye-blinking responses since cornea and conjunctiva are particularly sensitive to such stimulation. Uncontaminated OEPs can be expected only when no chemical stimulation occurs at the eye. Moreover, eye-blinking is also elicited by chemical and mechanical stimulation of the nasal mucosa.

Smith et al. (1971) suggested that there were no olfactory EEG responses and that all OEPs, including those reported by Finkenzeller and by Allison and Goff, were produced by chemical irritation of the intranasal free trigeminal nerve endings. To support their suggestion, Smith and his group reported on results obtained on patients who had lost trigeminal sensitivity on one side of their nose. In those cases they were not able to find EEG responses to odorous substances. It is our opinion, however, that odorous substances produce both olfactory and somatosensory evoked potentials in man and animals. In the second part of this paper we will present suggestions that olfactory and somatosensory responses are separate phenomena that might be differentiated both in terms of their topographical distribution on the skull and in terms of the time course of the adaptation of each.

In regard to the third requirement cited above the repetitious presentation of an olfactory stimulus to improve signal-to-noise ratio causes serious difficulties when studying olfaction due to the rapid and significant adaptation and habituation that occurs. As a result, in most experiments that have been reported, no more than thirty consecutive stimulus presentations have been used. Knowledge of the time course of adaptation and habituation for the different components of the OEP is considered to be particularly important in these considerations.

STIMULUS DEVICE AND CONTROL OF ARTIFACTS

The "pulse method" of presenting odorous substances has been one of the more common techniques of olfactory research on animals. The method involves typically the presentation of an air-puff that is blown towards the olfactory mucosa. The air-puff can be varied in its duration, and the concentration of odorous substances con-

tained within it can be controlled (e.g., see Giesen and Mrowinski, 1970; Herberhold, 1973). The major advantage of the pulse method is that the stimulus onset time is very rapid. The maximum concentration of odorous substance can be reached in approximately 20 msec (Plattig and Kobal, 1977; Kobal and Plattig, 1978).

The major disadvantage of the pulse method is that, inherently in its use, it elicits strong, artifactual nonodorous responses which are synchronized to the presentation of the odorant. The only method of stimulus presentation, in our opinion, that completely avoids this artifact is the "flow method" of stimulation. In the flow method a constant gaseous flow continuously flows over the nasal mucosa. At the time of stimulus presentation an odorous substance is substituted for the neutral gas without altering the rate or volume of air flow. The major difficulty of the flow method, of course, is to develop an ability to substitute the odorant substance for the neutral gas in such a manner that the maximum concentration is reached rapidly and yet no flow turbulences are generated.

The olfactometer developed in our laboratory is illustrated in Fig. 1. When using the flow method compressed air is cleaned and dried with charcoal and CaCl_2 and then delivered to three air cylinders. Prior to the observation interval when an odorous stimulus is presented, clean air is delivered via Tube C (Control) to Flask I which contains distilled water. The air is then delivered from the air cylinder to the most important part of the olfactometer - the 3-Y shaped nasal exit - where it is presented to the human observer. During this period in which neutral air is being delivered to the nasal exit all other (odorous) air is exhausted via Tube E_1 . In order to present an odorous stimulus with a controlled concentration, clean and dried air is delivered via Tube O (odorant) to Flask II containing the odorous substance. If maximum saturation of this odorant is required, the air is delivered to the nasal exit in an undiluted form. During the presentation of the odorant, the neutral air that had been delivered to the nasal exit is exhausted from the nasal exit via Tube E_2 . The switching of the exhaust tubes from E_1 to E_2 is accomplished with a magnetic valve (M) also developed in our laboratory. If an odorous substance with a lower-than-maximum saturation is required, the odorous air from Flask II can be diluted by replacing part of the air with neutral air from Flask III. To do so, a volume of odorant air equal to that being added from Flask III is exhausted from the output of Flask II via Tube E_0 . In this manner any saturation of odorant from 0% to 100% may be delivered at the nasal exit.

All tubing in the olfactometer is constructed of teflon or glass. A thermostabilized water cover keeps the temperature of all tubing at a constant 37°C . At the beginning of the observation

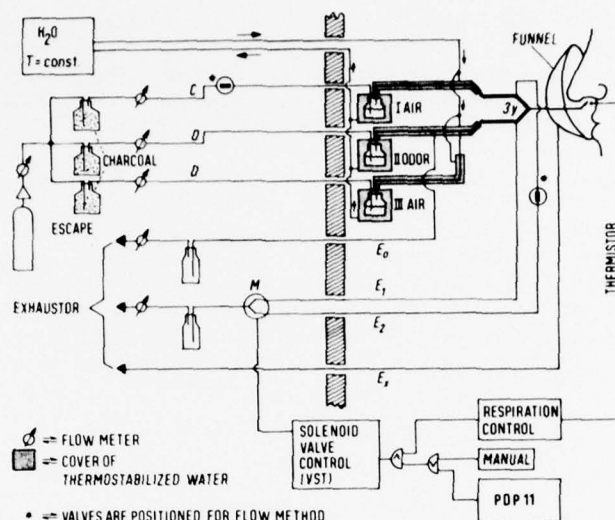


Fig. 1. Olfactometer for both the flow method and the pulse method. To use the pulse method the two valves designated by asterisks have to be closed, but to use the flow method they have to be open so that the path C-Flask I- E_2 can be opened by the magnetic valve M while E_2 is closed. Flask I and Flask II contain distilled water and Flask III the odorant

interval, when the odorant air is substituted for the neutral air, the air exhausted from the nasal exit via E_2 is equivalent in flow and temperature to that being delivered at the nasal exit from Flask II (and III). The odorant air reaches the nasal cavity 2 msec after the neutral air is replaced by the odorant air at the input to the nasal exit. Because of the effectiveness of the air flow system and the magnetic valve, it is possible to select a stimulus onset time as fast as 40 msec when using the flow method. Even at the maximal flow rate of 500 ml/sec no flow turbulences are observed when a 40 msec rise-fall time is employed.

In our research the nasal exit terminates in a funnel located directly, but loosely, in front of the observer's nose and is connected to an exhaustor. When using a prenasal application, however, it is necessary to initiate each stimulus presentation at the same moment in the inhalation process. For this purpose a thermistor located directly in front of the nose and a suitable electronic circuit are used to synchronize the respiration cycle and stimulus presentation. The disadvantage to this synchrony, of

course, is the confounding that occurs due to the recording of extra- or intracranial potentials associated with respiratory activity. These confounding effects can be minimized (Kobal and Plattig, 1978).

The olfactometer may also be used in the pulse method of stimulation. By switching the valves on Tubes C and E₂ (designated with asterisks in Fig. 1) the continuous flow of neutral air prior to and following the presentation of the odorant are eliminated. In addition, the rise-fall time of the stimulus may be reduced to approximately 20 msec when using this method.

During stimulation the clicking noise of the valves and, when using the pulse method, the hissing sound generated by the air flow may be masked by white noise presented via headphones.

Typical results obtained while using the olfactometer in both the flow method and the pulse method are shown in Fig. 2. Trace 1 (the upper trace) shows the resulting waveform that occurred when nonodorous air was presented to the observer via the flow method. As can be noted, no meaningful potentials occurred. Trace 2 shows the results obtained when eucalyptol was presented to observers using the flow method. Definite positive and negative deviations with readily measurable latencies occurred. Trace 3 shows the results obtained in response to nonodorous air when using the pulse method of stimulation. *The potentials seen are the result of tactile somatosensory stimulation.* Trace 4 indicates the results in response to eucalyptol when using the pulse method. The potentials were somewhat different than those elicited by the same odorant when using the flow method. The magnitude of N1 was noticeably smaller, and the latency was approximately 20 msec shorter. These differences resulted presumably from the interaction of the positive component of the somatosensory potential and the negative deviation of the olfactory response. Further, since the influence of the tactile somatosensory potential is not always phase-coherent to the olfactory response, the shape of the resulting potentials varies considerably. This variance eliminates the possibility of a meaningful evaluation of amplitudes or areas of the potentials when using the pulse method.

Table I summarizes the latencies for the various positive and negative potentials that occurred in response to the eucalyptol in the flow method conditions.

Another source of artifact cited earlier was the central and peripheral potentials associated with eye-blinking. The presentation of high concentrations of an odorant often elicits eye-blinking responses, particularly in the early minutes of a data gathering session. The associated electrical activity (e.g.,

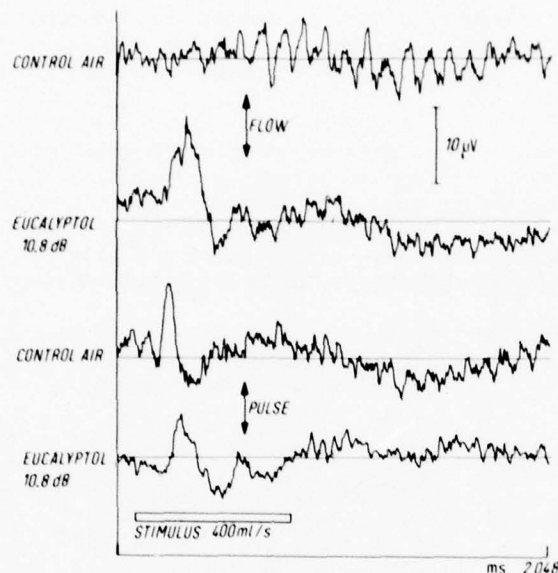


Fig. 2. Comparison of OEPs obtained by the flow method (trace 1+2) and by the pulse method (trace 3+4). Lead Cz/Al. Negativity up. N=16. Likewise in all following records.

the electronystogram record, ENG) usually results in a positive potential (approximately 200 uV) when the record is obtained at the vertex (EEG position Cz/Al). The interaction of the ENG and the OEPs may result in a variety of distortions depending upon the

Table I. Average latencies for OEPs from Cz/Al of twelve subjects. The mean latency and the standard deviation (\pm s) in msec for twelve subjects are indicated. Each individual subject's waveform represented the averaged result of sixteen stimulus presentations. The latency values shown include the physiological time for excitation and conduction as well as the stimulus transportation time from the prenasal thermistor to the olfactory epithelium. Although results for only one stimulus intensity (12.04 dB re threshold) are shown, other results indicated that the latency of the OEP was dependent upon stimulus intensity.

P1	N1	P2	N2	P3
222.2 \pm 46.0	317.2 \pm 31.9	455.7 \pm 43.2	572.7 \pm 47.3	695.0 \pm 64.4

phase relations of the two potentials. Frequently an increase in the magnitude of P2 is seen, and occasionally the complete masking of N1 occurs. As a result we have adopted a procedure (OFFLAB) developed by Spreng (1976) to eliminate or minimize the contribution of artifacts to the evoked potential record (Kobal and Plattig, 1976).

An added benefit of the application of the OFFLAB program to eliminate contamination from eye-blink is that contamination from other sources may also be eliminated. Gaardner (1964), for example, has described the visual evoked potentials associated with eye movements. We consider, then, the method of averaging only uncontaminated OEPs to be the most reliable procedure currently available.

CHEMICAL STIMULATION OF THE TRIGEMINAL NERVE

Many substances that evoke an electro-olfactogram (EOG) in experiments on animals excite the trigeminal nerve by stimulating its free nerve endings. Beidler (1965) demonstrated this by recording the activity of small branches of the trigeminal nerve while stimulating the nasal epithelium. Dawson (1962) was able to record electrical activity in the trigeminal nerve while chemically stimulating the cornea of the rabbit. In unpublished experiments in our laboratory we have recorded local potentials from the cornea of the frog while stimulating the cornea and conjunctiva with linalool and eucalyptol. The local potentials resemble closely the EOG potentials in shape but have a positive deviation rather than the negative potential of the EOG. The amplitude of the potential is dependent upon stimulus intensity and has an initial latency of about 2 sec (slightly longer than the corresponding peak of the EOG).

This direct stimulation of the trigeminal nerve by odorants has long been a difficulty for scientists studying the olfactory system. Tucker (1971) suggested: "The dream of finding an odorant that is purely olfactory in its stimulating capabilities is still unrealized." Smith (1971), as discussed earlier, argued that "olfactory" potentials are elicited solely by the excitation of the somatosensory modality. In our opinion this discussion of olfactory and somatosensory interaction will continue until a patient whose trigeminal sensitivity is completely lost can be examined. Unfortunately no such opportunity has as yet arisen for us. We have, however, examined patients whose filia olfactoria were torn off following aneurismorrhaphy. In these patients we found a distinct decrease in the amplitude of evoked potentials recorded in response to odorants on the affected side. We presume, in these patients, that both the olfactory and somatosensory modalities were responsible for the recorded activity.

To examine this problem further we have performed the following experiment. A thin teflon tube, 2 mm in diameter and connected to the olfactometer exit, was inserted into the nose approximately 2-3 cm. The air flow was directed either through the lower nasal duct (Condition A) or towards the olfactory cleft parallel to the dorsum of the nose (Condition B). This procedure was repeated on both the left and right sides. Amyl butyrate and eucalyptol were used as odorous stimuli. The evoked potentials based on sixteen stimulus presentations in each condition are shown in Fig. 3. In each case the potentials recorded in Condition B were greater in amplitude. Further, and particularly when amyl butyrate was presented, an additional potential component appeared approximately 300-400 msec after the onset of the stimulus (either another peak was discernible or the existing peak broadened in shape). The subjective responses reported in the two conditions were noticeably different. In Condition A the cooling effect of eucalyptol was felt in the "lower" part of the nose. In response to the amyl butyrate the subjects reported the odor of raspberry but were unable to localize the sensation. In Condition B the sensation of the two substances was more "upward" in the nasal cavity. Further, the subjects reported that the perceptions that occurred in Condition B suggested the stimulus had a much sharper ("steeper") rise time than the perceptions elicited in Condition A.

Also shown in Fig. 3 are results obtained in Condition A in response to eucalyptol following the application of a local anesthesia to the lower and middle nasal duct. The resulting evoked potentials were considerably smaller in amplitude except for an unusual characteristic. Following a substantial delay, a late positive potential appeared. The potential occurred according to a perception reported by the subjects that was localized in the pharynx.

Two possible explanations for the data reported in the experiment described above are noteworthy. First, it was our intent to vary the manner in which the odorant reached the olfactory mucosa. In Condition A we imagined the odorant would infiltrate upwards relatively slowly through the nasal cavity. In Condition B, however, we were assuming the odorant would reach the olfactory mucosa more directly and more rapidly. The perceptual results of the experiment as reported by the subjects apparently confirm our intentions. Further the electrophysiological results suggest that the rise-time of the stimulus may be of critical importance in determining the magnitude of the OEP.

Another explanation of the potentials shown in Fig. 3 is that stimulation in Condition B may have elicited responses in trigeminal receptors that are different from and more sensitive than those receptors stimulated in Condition A. Finally the results reported

in this experiment may also help account for the negative results reported by Smith, et al. (1971). Using the flow method of stimulation the design of their olfactometer required a large volume of gas resting in the odorous cylinder to be accelerated and then transported a considerable distance to the subject. As a result the onset time of the stimulus may have been too slow to elicit the OEP.

DISTRIBUTION OF AMPLITUDES AND LATENCIES ON THE HUMAN SKULL

As suggested in the introductory remarks, an examination of the topographical distribution of evoked responses on the human skull may provide information helpful in the separation of ol-

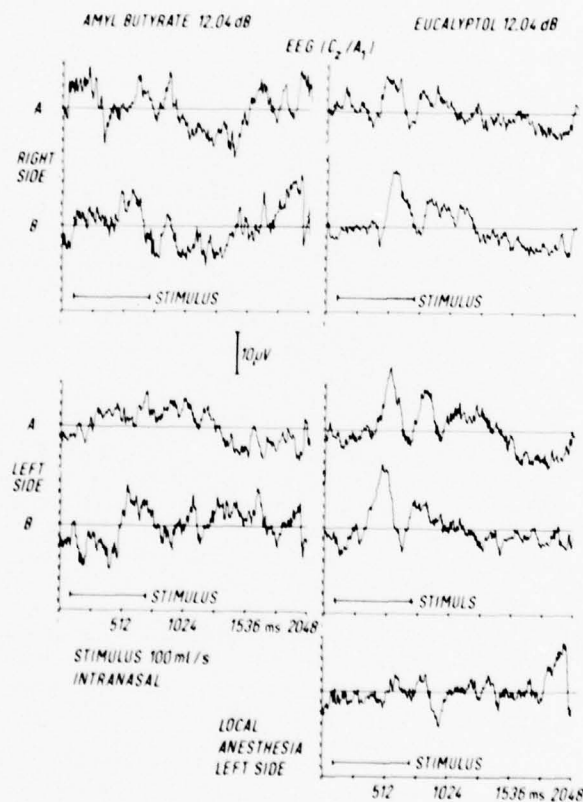


Fig 3. AEPs after stimulation of the lower (A) and of the upper (B) parts of the nasal cavity by amyl butyrate and by eucalyptol.

factory and somatosensory responses. Additionally information provided by such an analysis can be used to determine the optimal number of recording sites that should be employed in the measurement of OEPs.

To conduct such an examination EEG records were obtained at nineteen positions (on the 10/20 classification) on the skull in response to eucalyptol presented at the right nostril via the flow method. The recordings were made in two separate sessions. In the first session ten positions in the frontal part of the skull were used. Eight positions in the rear of the skull were examined in a second session. In addition, position Cz (vertex) was included in both sessions for comparison purposes. Position A1 (the left mastoid) was the reference point for all positions. All EEG records were recorded on a 12-channel Siemens-mingograph as well as stored on magnetic tape (Sangamo Sabre VI: PCM by Johnne and Reilhofer 3K12).

Ten subjects were initially employed in the experiment. Three of the ten subjects had to be eliminated due to heavy eye-blinking. Of the remaining seven subjects, five were examined in all conditions on two separate sessions (i.e., the recordings on both the frontal and rear positions of the skull were repeated). The remaining two subjects were examined entirely on one occasion. An overload of artifactual components required the omission of some of the sessions. As a result final data analysis was computed on eight sessions recorded at the frontal sites and eleven sessions recorded at the rear positions. A further complication resulted when some of the recording sites yielded no measurable potentials (or a minimal number of non-zero values). As a consequence no analysis of variances could be employed.

Some of the results of the experiment are shown in Fig. 4. At the upper left position of the figure a typical evoked response is illustrated. Additionally the N1/P2 amplitude (a), the P2/N2 amplitude (b), the area under N1 (F1) and the area under N2 (F2) are illustrated. At the lower left of the figure are the evoked potentials obtained on one subject at both the frontal sites (lower) and the rear sites (upper) on the skull. On the right side of Fig. 4 are the results of the amplitudes and area measurements. Under "a" are the N1/P2 measurements summarized on a 9-point scale from black (maximum amplitude) to white (minimum amplitude). The results under "b" summarize the P2/N2 amplitude measurements, etc. The illustration of each skull is divided into a 5 x 5 matrix which corresponds to the international 10/20 classification. The illustration immediately under "a" and "b" (row 1) summarizes the results obtained at the frontal positions, and the illustrations just below (row 2) summarize the results at the rear positions. The combined results are shown in row 3. The results of the area measurements

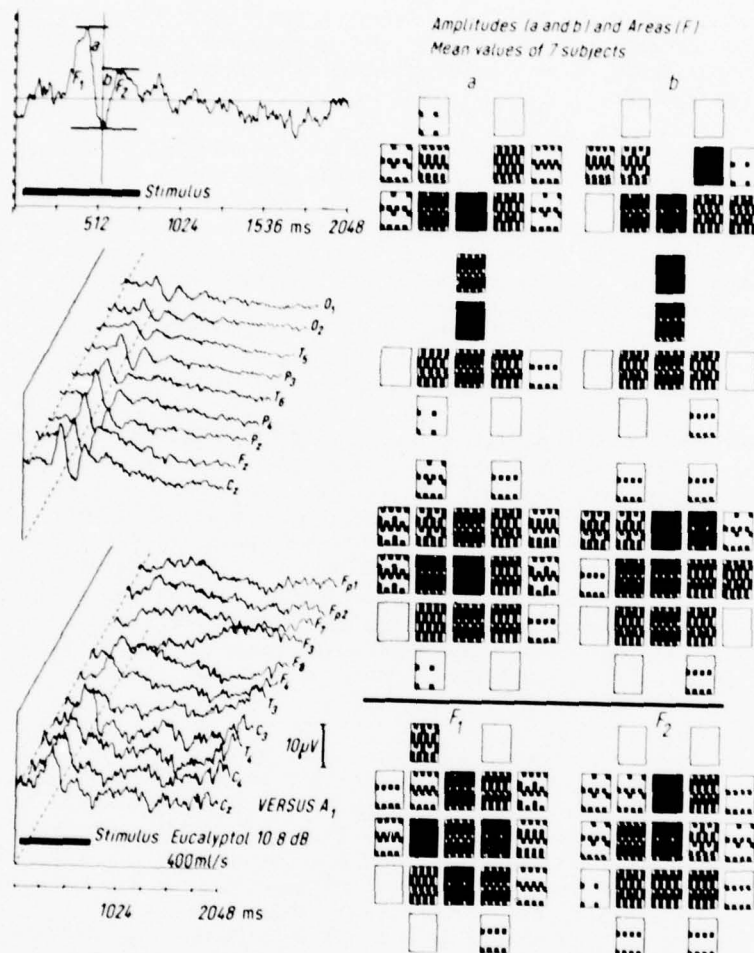


Fig. 4. Distribution of amplitudes and areas of OEPs (maximum black).

have been combined into the row four illustration (even though they are collected in two separate sessions). The results shown in Fig. 4 are the mean values for seven subjects.

In general the late unspecific potentials reached their greatest amplitude at recording sites near the vertex. The maximum N1/P2 amplitude occurred directly at the vertex, and the second highest amplitude occurred at C3 (the position adjacent to the ver-

tex and contralateral to the stimulated nostril). The maximum P2/N2 amplitude occurred at Fz and F4. The results of the measurements of the area under N1 and under N2 were distributed similarly to the amplitude results.

The upper half of Fig. 5 summarizes the results of amplitude measurements of each of the five identifiable peaks (P1, N1, P2, N2, P3) when the measurements were made from the "baseline of the EEG". The baseline, illustrated as a straight horizontal line in the evoked response shown in Fig. 4, is the linear average of each EEG record. The results shown in Fig. 5, like those in Fig. 4, are the mean values obtained from seven subjects. The results indicating the distribution of amplitudes on the skull for N1 are similar to the distribution measured on N1/P2. Further, the topographical distribution of N2 was similar to that for N2/P2.

Results concerning the averaged latencies for the five peaks (P1, N1, P2, N2, P3) relative to the onset of the stimulus are summarized in the lower half of Fig. 5. Again a 9-point scale from black (maximum latency) to white (minimum latency) was employed. An examination of these results points out that, at least for the N1 and N2 peaks, the topographical distribution of the minimum latencies is similar to the distribution of the maximum amplitudes (and, conversely, maximum latencies are similar to minimum amplitudes). The relationship between the topographic distribution of amplitudes and latencies for the other peaks (P1, P2, P3) is more complex.

The results displayed in Fig. 4 were submitted to a factor analysis (diagonalization method, varimax rotation), omitting those positions which sometimes yielded no measurable potentials. Although the results of the analysis for the amplitude and latency measures of each component of the potentials are too numerous to summarize in this paper, several results were noteworthy. In the examination of the topography of the N1 potential (amplitude), three factors with loads greater than 0.7 ($p < 0.05$) were noted. Factor I pointed towards the central positions (loads: -0.96 for Cz, -0.95 for C3); Factor II to the precentral positions (loads: 0.82 for T4 and 0.86 for F3); Factor III to the contralateral positions (loads: 0.89 for F7 and 0.90 for T3). Similar results and loads were obtained when the latency of N1 was analyzed. In our opinion these results suggest the presence of three underlying variables. The first relates to the central positions (vertex), the second to the precentral positions and the third to the left-right displacement.

When the amplitude of N2 was examined similarly, three factors were again extracted. They also exhibited loads of similar magnitude (Factor I: 0.92 for Cz, 0.84 for C4 and 0.79 for C3; Factor II: 0.89 for T3; Factor III: 0.71 for T4). The results of the

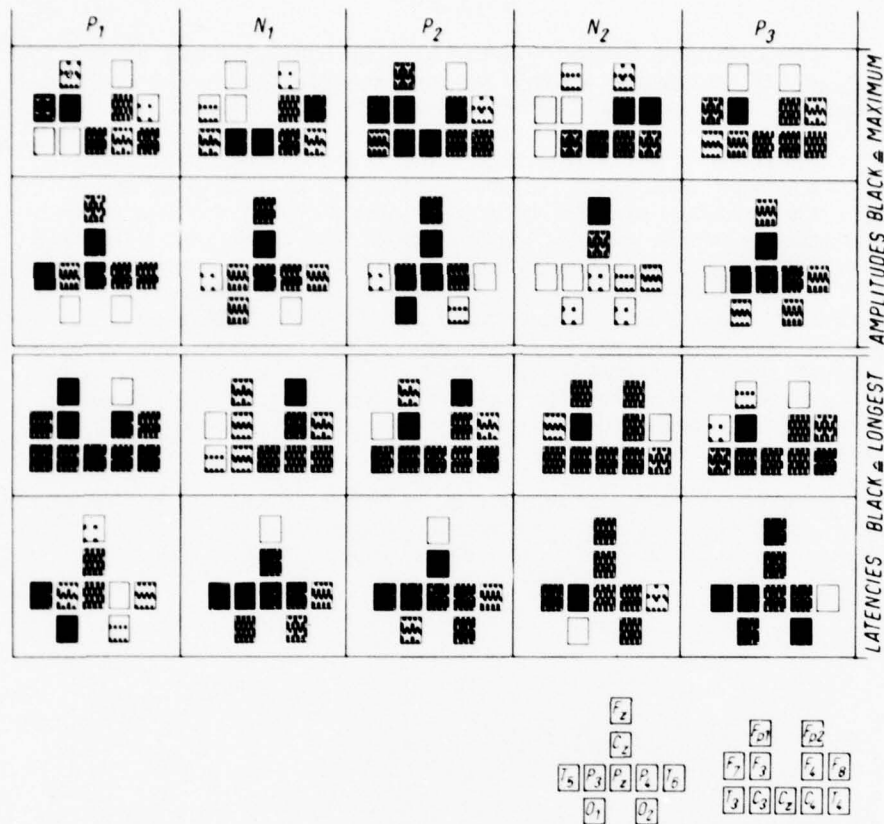


Fig. 5. Distribution of amplitudes and latencies of OEPs (maximum black).

analysis of the latency of N2 were similar. Again we interpret these results as suggesting the presence of three underlying variables which relate to the central positions, to the left side and to the right side.

The analysis of the potentials (amplitude and latency) on the occipital parts of the skull brought up only one factor. The factor corresponded quite nicely with the distribution of the OEPs which become smaller as the electrode is moved in an occipital direction (see Fig. 4).

CONCLUSION

Although much research remains to be completed and we are only at an intermediate point in our investigations; the results obtained thus far permit several tentative conclusions.

First it is quite clear that the topographical distribution of the evoked potentials on the skull are a nonrandom arrangement that reach a maximum at or near the vertex. The amplitude and latency of the various components of the potentials displayed relatively specific patterns in response to stimulation by eucalyptol at the right nostril. Our hypothesis that the OEP reflects activity from both the somatosensory and olfactory systems, however, has not yet been completely confirmed. Nevertheless, our results suggest there is probably more than one generator responsible for the evoked potentials. The exact number of generators and the underlying systems to which they are associated remain to be verified.

Although the topographical arrangement of the OEP on the skull is quite complex, our results suggest that only two electrodes are necessary to record representative OEPs. To do so, one

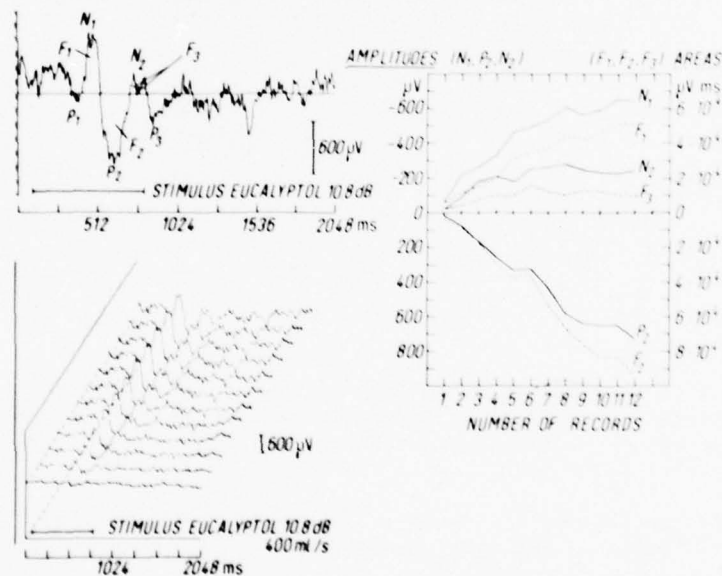


Fig. 6. Time course of single components of OEPs during averaging Cz/Al.

electrode should be located at Cz and the other at a precentral position (e.g., F4). Of course, for omitting eye-blinking artifacts as discussed earlier it is also necessary to record the ENG potentials.

Finally, we feel that further confirmation of our hypothesis concerning the generators of the OEP may be gained by examining the time course of adaptation of the various components of the OEP. The details of an experiment we are conducting currently and some early results are shown in Fig. 6. Briefly, we are examining the changes in amplitude that occur in N1, P2 and N2 (designated on the upper left of Fig. 6) as well as the changes in the magnitude of the areas of N1 ("F1" in Fig. 6), P2 ("F2") and N2 ("F3") as an odorant is presented twelve times in succession. The odorant we are examining is eucalyptol at an intensity of 10.8 dB re threshold. The interstimulus interval in the succession of twelve presentations is 50-60 sec.

A cumulative record of the EEG recordings made on one subject during a single session are shown in the lower left portion of Fig. 6. The lower record was elicited in response to the first presentation of the stimulus; the second record is the cumulative EEG response to the first two stimulus presentations, etc. The twelfth record, then, is the cumulative EEG of all twelve stimulus presentations. On the right-hand side of the figure some of our results are summarized. Each function displays the cumulative result that occurred during the twelve presentations of the odorant. The amplitude values are displayed on the left ordinate (for N1, N2 and P2) and the area values for N1 (F1), P2 (F2) and N2 (F3) on the right-hand ordinate. (A cumulative function that increased linearly throughout the twelve presentations would indicate that the component being measured remained constant in response to each stimulus presentation. A horizontal cumulative function would indicate the component had disappeared.)

Several interesting findings can be noted. For example, the amplitude of the N1 wave remained relatively constant throughout the first five presentations of the stimulus, was somewhat reduced in magnitude through the eighth presentation and had completely adapted and disappeared during the latter presentations. The amplitude of the P2 wave, on the other hand, remained relatively constant throughout the twelve stimulus presentations. The magnitude of the N2 wave, in contrast, seemed to oscillate somewhat during the session. The results of the area measurements indicated a pattern of adaptation similar to that exhibited by the amplitude measures.

At the present time we are making similar analyses on data collected on many subjects in several experimental conditions. We continue to believe that the time course of adaptation of the

various components will be useful in distinguishing those aspects of the OEP attributable to the somatosensory system and those parts resulting from olfactory processes.

SUMMARY

An improved device is described for olfactory stimulation via: (a) the "pulse method", and (b) the "flow method". Only the flow method (with stimulus onset and offset times of 40 msec each) guarantees reproducible records of olfactory sensory activity by avoiding mechanoreceptive artifacts; additional control of thermoreceptive, auditory and eye-blinking artifacts is necessary. Human olfactory evoked responses from nineteen different sites of the skull are demonstrated. The components N1, N2 and P2 with different rates of adaptation are more clearly recognizable than P1 and P3. N1 (which is possibly of somatosensory origin) occurs 270-350 msec, N2 (possibly of olfactory origin) 520-620 msec and P2 occurs 410-500 msec following the stimulus onset. The maximum amplitude of N1 is recorded in the central, contralateral (to the stimulated nostril) area of the skull and the maximum of N2 is found at the precentral ipsilateral area.

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EVENT RELATED SCALP POTENTIALS DURING A BIMANUAL CHOICE R.T. TASK:
TOPOGRAPHY AND INTERHEMISPHERIC RELATIONS

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INTRODUCTION

The general purpose of this experiment is to evaluate the specificity of electrophysiological correlates of decision making in the brain; in particular, its main goal is to investigate possible relationships between right and left hemisphere scalp recorded electrical activity during a choice reaction time task and either the stimulated or the responding side of the body.

Much work has recently been devoted to the study of electrical correlates of preparatory mechanisms before movement. In man, tools for investigation range from purely behavioral (RT and performance) to scalp recorded EEG activities (readiness potentials, premotor and motor potentials, contingent negative variation, the P300 wave of the evoked potential, etc.) through electromyography and other indexes.

The readiness potential (RP), a large negative shift, appears on the scalp prior to a voluntary movement (Kornhuber et al., 1965; Gilden et al., 1977; Vaughan et al., 1968; Deecke et al., 1968; Gerbrandt et al., 1973). It is well established now that the final phase of this component and the motor potential (MP) (also negative) that occur during the movement tend to peak precentrally on the scalp contralaterally to the part of the body involved in the movement (Kutas and Donchin, 1977). This negative phase is followed by an abrupt positive postmovement deflection called the "reafferent potential".

If the preparatory stimulus warns the subject that he will have to make a movement with the right hand on the arrival of the imperative stimulus, the negative shift appears larger in the left hemi-

phere and vice versa (Syndulko and Lindsley, 1977).

The P300 (latency 250-500 msec), a late component of the sensory evoked potential, appears, or is greatly enhanced, if the stimulus is task relevant (Sutton et al., 1967), or uncertain (Sutton et al., 1965), rare (Cooper et al., 1977; Squires, 1977), if it is expected but does not occur (Weinberg et al., 1970; Simson et al., 1976; Renault and Lesevre, in press; Klinke et al., 1968; Renault et al., in press) or if the occurring stimulus is different from the expected stimulus (Demaire and Coquery, 1977; Courchesne et al., 1975). If visual stimuli are delivered in random order either in the right or left peripheral visual field, and if the subject is required to respond only to one of these stimuli, the components of the VEP, and the P300 in particular, appear enhanced after the presentation of this stimulus (Van Voorhis and Hillyard, 1977).

The above mentioned studies demonstrate that the topography and amplitude of both the CNV in preparation for a motor act and the P300 following the reception of an expected stimulus depend on afferent (sensory) and efferent (motor) information. The present study investigated whether any of the electrical events occurring between the stimulus and the response during a bimanual choice RT task were correlated, either with the responding hand or with the stimulated side of the body. Because the stimuli are task relevant, this experimental paradigm was expected to induce P300 components.

This situation was, however, preceded by a simple, self-paced movement task in order to compare the electrical pattern due to a complex stimulus-response paradigm to that produced by the movement alone.

EXPERIMENTAL PROCEDURE

General Setup

Four male and three female volunteers, aged 21-32, all right-handed, served as subjects for the experiment. Handedness was determined using a playing card dealing test (Zazzo, 1960); all subjects used the right hand spontaneously to perform the test, and dealing duration was more than twice as long when they were asked to employ the left hand instead of the right hand.

Subjects were seated in a comfortable chair in a dark, sound attenuated room; they were asked to relax all muscles as much as possible, contracting only those involved in the motor act. The movement consisted in a right or left index finger press on a micro-switch. Pressure required for contact closing was 300 ± 20 g, and

displacement of the index finger was 3 mm. Switches were fixed on a light cardboard cylinder grasped with both hands by the subject and resting on his knees. In order to avoid any auditory feedback from the switch operation, earplugs were worn by the subjects. Similarly a small luminous cross was used as a gaze fixation point to prevent eye movements during stimulation.

Scalp potentials were recorded with seven collodion-affixed Beckman electrodes placed along a transverse line running between two points situated 1 cm in front of the auditory canal via the vertex. This electrode placement was chosen in order to detect both motor potential components and P300s, and especially to evaluate their lateral topography. Interelectrode distance was 3.5 cm, and the mean of the two earlobe potentials was taken as a reference. Simultaneous vertical and horizontal electro-oculograms were also recorded; this permitted the elimination from the average of all self-paced movements or responses which were affected by eye movements.

The time constant of the EEG channels was 1.5 sec; the time constant of the oculogram, .3 sec. Analog-to-digital conversion was performed on-line; data were stored on digital tape and processed later by computer (BGE M40).

Self-Paced Movements

The task consisted of a self-paced, right and left index finger pressing on the microswitch. A regular pace of 2 sec was required in order to compare the situation with the reaction time procedure, and subjects succeeded in keeping this pace within reasonable limits (1.8 to 2.5 sec).

Choice Reaction Time Situation

The stimuli consisted of a brief flash (3 msec duration) from light emitting diodes placed on a panel standing approximately 40 cm in front of the subject. These stimuli appeared within a fixed period (2 sec) and, at random, either 10° to the right or the left of the fixation point; their color also varied randomly, either red or green. The subject was required to press with the right index (R) if the light flashed green and with the left index (L) if it flashed red, irrespective of the location of the stimulus [on the right (r) or on the left (l) of the fixation point].

Consequently the four possible situations that appear randomly can be labeled LR, RL (when the response must be given contralaterally to the stimulus), RR and LL (if the response is to be given on the same side as the stimulus). Prior to event related potential

recordings, subjects were given practice runs. Error-free performance was achieved after an average of twenty to thirty trials.

DATA ANALYSIS

Computer Data Processing

After suitable filtering (elimination of 50 cycle interference), responses were averaged, and spatiotemporal (equipotential) maps were plotted (Remond, 1961). Each map is the average of seventy to ninety responses, and the time reference (trigger) corresponds to contact closing of the index operated microswitches.

Statistical Analysis

The data between subjects exhibit large standard deviation interindividual variabilities which are greater than those due to differences between situations; in this case, a good practice is to calculate differences between situations for each subject and then to test whether the mean of these differences is statistically different from zero or not. The data obtained here exhibit Gaussian distributions, and samples are independent; it is, therefore, legitimate to use Student's "T" for comparisons. Data were also analyzed with a nonparametric sign test.

RESULTS

Self-Paced Movements

In agreement with the literature, all subjects exhibited a large negativity before the movement and a positive wave after the movement. However, interindividual differences between spatiotemporal characteristics were important and appeared largest when compared to intersituation (right or left index flexion) differences. Typical spatiotemporal maps of these results are shown in Fig. 1.

The premotion negativity (readiness potential or "RP") started at a mean latency of 200 msec before the motor act, slowly rising towards a peak culminating approximately 30 msec after the motor act. This peak, called motor potential (MP), appeared significantly contralateral to the movement ($t = 3.45$, $p < .02$) with a Student's test, and $p < .05$ with a sign test; see Table I and Fig. 2).

For six subjects out of seven, the amplitude of the MP was larger during the left-hand movement; this result is not, however,

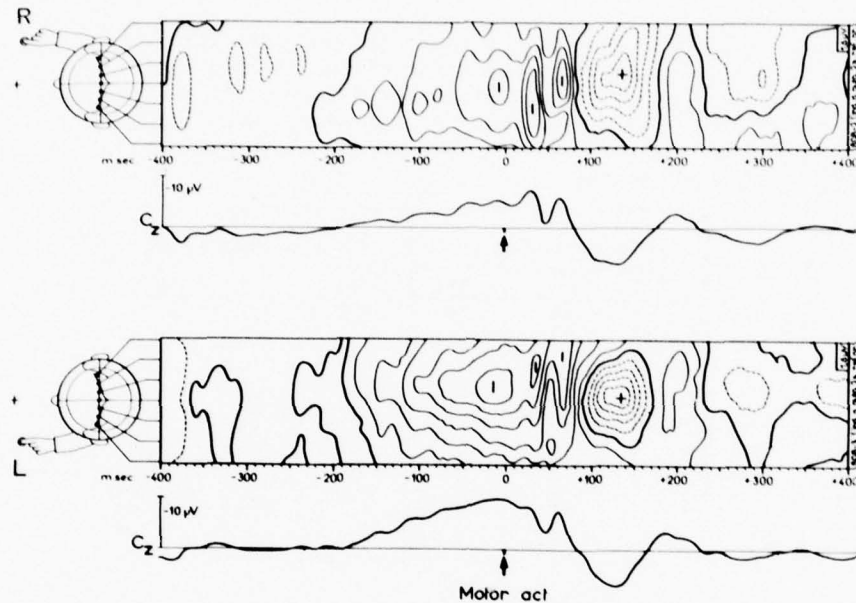


Fig. 1. Spatiotemporal maps during a self-paced right (R) and left (L) index flexion. Underlying chronogram represents activity at the vertex electrode. Average responses of eighty movements, at a rate of approximately 2 sec, triggered on the mechanogram. 1.6 μ V potential difference on all maps between two successive isopotential lines; linked earlobe references; + and - signs indicate peaks or dips of potential.

statistically very significant ($t = 1.99$, $p < .10$ with a Student's test).

The MP was sometimes preceded by a relative positivity (subjects ER, BG, CR) occurring just during the motor act and called premotion positivity (PMP). However, this event was not reliable enough to be taken into account in the present analysis.

The positive component that followed movement completion, called the "reafferent potential", appeared bilaterally distributed, except for subject RR for whom it peaked contralaterally to the movement. Its mean latency was 140 msec after the motor act with very small variability.

Table I. Experimental data for right (R) and left (L) index self-paced flexions: Topography and amplitude of MPs for the seven subjects. Mean and SP values are plotted in Fig. 3, whereas mean differences are used for statistical analysis. Topography is referred to Cz counted positive towards the right hemisphere and negative towards the left.

	MP topography (cm)			MP Amplitude (μ V)		
	R	L	R-L	R	L	R-L
ER	-4	+6	-10	-7.8	-10.0	+2.2
BG	-1.5	+2	-3.5	-4.0	-7.0	+3.0
GG	-1	0	-1	-4.3	-4.3	0
CR	-1	+4.5	-5.5	-3.8	-8.0	+4.2
AA	-3	+5.5	-8.5	-6.4	-10.0	+3.6
RR	-1	+4	-5	-4.9	-2.1	-2.8
JMA	0	0	0	-1.8	-4.5	+2.7
Mean	-1.6	+3.1	-4.78	-4.7	-6.6	+1.84
S.D.	1.4	2.5	3.66	1.9	3.0	2.44

Choice Reaction Time Task

During this task a few errors (response given with the wrong hand) occurred (one out of eighty responses, approximately). These were not taken into consideration and were deleted from the average.

In all possible situations, LR, rL, rR, lL, i.e., irrespective of the stimulus color and location, all subjects produced a large positive wave between the stimulus and the response with a mean latency of approximately 370 msec (Fig. 3).

These P300 waves were sometimes followed by a small relative negativity. This event exhibited the same latency as the motor potential of the corresponding self-paced motor potential for a given subject.

When detectable, this negativity was followed by a further positive event that peaked on the vertex (subjects ER, BG) or appeared contralateral to the movement (subjects AA, RR) with a mean latency of about 140 msec after the motor act. The topography and latency of this component was similar to those of the reafferent potentials observed during the self-paced movement.

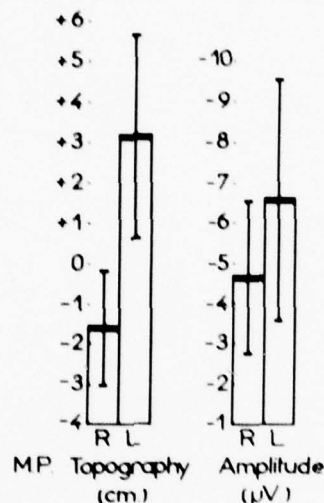


Fig. 2. Average topography and amplitude of MPs for the seven subjects. Topography is counted positively towards the right hemisphere and negatively towards the left with respect to Cz. MP maxima are contralateral to the movement, and their absolute amplitude is larger for a left index flexion. Standard deviation is across the seven subjects.

The P300 waves reached their maximum amplitude later in the contralateral than in the ipsilateral situation (Table II and Fig. 4). This was observed in all subjects, the mean increase in latency being equal to 34 msec. This difference is statistically significant ($p < .05$ with sign test; $t = 5.44$, $p < .005$ with Student's test). Conversely, there was no marked difference in the latency of P300 with respect to the responding hand.

This difference in the latency of the P300 wave was accompanied by a similar difference (28 msec) in the reaction time between the contralateral and ipsilateral situations which was also observed in all seven subjects ($p < .05$ with sign test; $T = 5.27$, $p < .005$ with Student's test). These results are in agreement with purely behavioral experiments (Craft and Simon, 1970). The responding hand had no effect on the RT either.

Together with this effect on RT and latency of the P300 waves, the amplitude of the P300s was also modified; they appeared larger (mean amplitude equal to 10.9 µV with respect to the baseline) in the contralateral situation than in the ipsilateral situation (mean

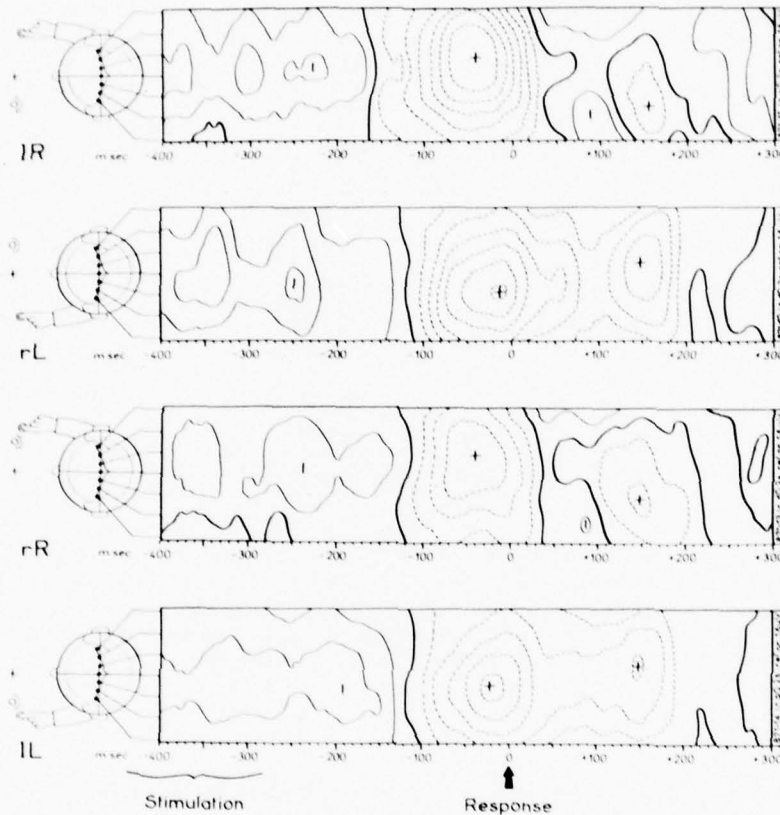


Fig. 3. Spatiotemporal maps during bilateral choice RT task. Stimulus appearing regularly every 2 sec, either in the right (r) or in the left (l) visual half-field, randomly and requiring either a right (R) or left (L) index flexion. Average responses to eighty movements triggered on the mechanogram; linked earlobe reference.

amplitude = 8.5 μ V). This difference was also observed in all seven subjects ($p < .05$ with sign test; $t = 8.77$, $p < .001$ with Student's test).

The responding hand had no marked effect on the absolute amplitude of the P300, but it modified the topographical distribution of the P300 wave which culminated slightly on the right (1.7 cm) of the vertex for a right hand movement and on the left (1.8 cm) for a left hand movement. These differences are significant ($p < .05$ with sign test; $t = 4.54$, $p < .005$ with Student's test).

Table II: RT, and latency, topography and amplitude of P300 peaks for the seven subjects in the four possible situations during the choice reaction time task.

	Reaction Time (msec.)			P300 Latency (msec.)			P300 Topography (cm.)				P300 Amplitude (μ V)						
	IR	RL	RR	IL	IR	RL	RR	IL	IR	RL	RR	IL	(IR+RL)/2 -(RR+IL)/2 Contra-Ipsi	(IR+RR)/2 -(RL+IL)/2 Right-Left			
ER	448	488	426	447	406	390	370	349	1	-1	0	0	9	9.2	6.2	6	3
BC	405	432	384	400	311	362	294	330	2	-1	2	0	10	12.5	6.5	10.5	3
CC	381	394	363	366	369	386	351	354	0	-1	0	-1	18	15.6	13.2	14	3.2
CR	414	374	398	340	346	394	314	300	5	0	5.5	-1	12.4	14.8	10.4	12.4	2.2
AA	422	391	400	394	318	379	356	372	3	-3	3.5	-2	10.8	9.8	5.8	8.4	3.2
RR	535	500	479	488	485	446	419	440	1	-4	1	-3	6.6	6	6.6	3.7	1.6
JMA	453	455	407	408	405	399	343	364	0	-4	1.5	-5	10	8	7.6	8.6	1.4
Mean	440	433	408	409	386	394	350	358	1.57	-1.86	1.93	-1.71	10.97	10.84	8.04	9.08	2.52
S.D.	51	49	37	45	55	26	40	43	1.90	1.77	1.99	1.80	3.57	3.57	2.74	3.57	0.76

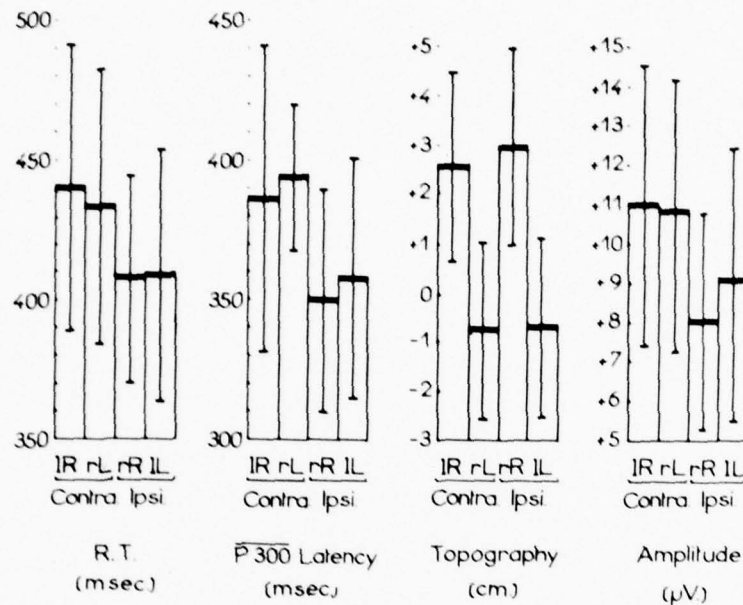


Fig. 4. Average RT, and latency, topography and amplitude of P300 peaks for the seven subjects. The topography of the P300s is ipsilateral to the responding hand. RT is longer in contralateral situations, together with the latency of P300 peaks. In the contralateral situations P300 amplitudes are larger.

DISCUSSION

In the RT situation subjects have to act in response to the color of the stimulus; here the movement programming is subsequent to a decision which requires a certain amount of information processing.

The electrical patterns observed on the scalp in this situation differ from the self-paced task mainly in that they all exhibit a large positive wave (P300) before the response. This P300 component seems to appear superimposed on the emerging negative readiness potential. In a few cases a slight negativity can be observed following the P300, and at the same latency, that of the self-paced motor potential. This could explain why the P300 topography appears to be dependent on the responding hand. Indeed, if the MP (negative) or the last part of the RP (also negative) does superimpose on the P300, partial cancellation would occur on the potentials recorded on

the hemisphere contralateral to the responding hand, thus making the P300 predominate on the ipsilateral hemisphere.

The P300s are much smaller, or even absent, with stimulus alone when no task is required (this well known fact has been verified in the present experiment for two subjects). Nor are these waves present during the self-paced task. Consequently they appear to reflect a decision-making process; if the P300 is accepted as being such an index of relevant response evaluation, then the results obtained in the present experiment can be explained as follows: in the contralateral situation longer RTs, accompanied with a longer P300 latency indicate (a) that the response takes more time for the subject to evaluate and (b) that the response is dependent on the P300.

Moreover, the fact that P300 amplitude is larger in the contralateral than the ipsilateral situation is an additional argument in favor of the above mentioned significance of the P300 index.

The logical relationship from cause to effect of this succession of events could be traced in this way: contralateral stimulus-response evaluation takes a longer time, this leads to a longer latency for the P300 and this, in turn, increases the RT. Why evaluation itself takes a longer time remains to be explained, but two hypotheses can be formulated:

- (1) Afferent information takes a longer time to reach the contralateral hemisphere (approximately 10 msec), but this fact alone cannot be responsible for the long difference observed concerning the P300 increase in latency (34 msec) as well as the RT increase (28 msec).
- (2) Innate and learned body responses are better organized to be carried out by the limbs ipsilateral to the stimulation (Simon, 1969); this would seem to be a logical process as a defense reflex or as a simple energy saving process.

CONCLUSION

A negative shift occurred prior to the self-paced movement becoming contralateral towards the end, and a positive shift followed the movement.

During the bilateral choice RT task the P300 culminated on the hemisphere ipsilateral to the stimulation; this could be the result of partial cancellation of the P300 and the negative MP on the hemisphere contralateral to the movement.

The contralateral situation appeared to have two significant

effects on the P300s: their latency was increased, as was the mean RT; their amplitude was also increased compared to that obtained in the ipsilateral situation. This can be explained by assuming that the P300 is an index of decision-making. A contralateral stimulus-response task, which is more difficult to evaluate (having larger P300s), takes more time for the decision to be accomplished (having delayed P300s) which, in turn, leads to a longer RT.

SUMMARY

This study was undertaken in order to investigate the specificity of the electrical events observed on the scalp during a choice reaction time task, particularly when the response is contralateral or ipsilateral to the stimulation.

Seven right-handed subjects were requested to press a switch as fast as possible with their right index finger in response to a green light and with their left index finger in response to a red light. These stimuli appeared at random, within 2 sec intervals and at a 10° angle, either on the right or the left of a fixation point.

For the seven subjects in these four situations, a large positive potential (P300) appeared, peaking approximately 50 msec before the response. This peak was shifted towards the right hemisphere before a right hand response and vice-versa. This result could be related to the fact that the ends of the readiness potential and the motor potential were contralateral to the movement, thus partially cancelling the P300 contralaterally to the response.

The latency of this P300 was longer in the contralateral situation, as was the RT; also the amplitude of the P300 was larger in this case with respect to the ipsilateral situation. Consequently the P300 latency and amplitude appear as electrophysiological indexes of the difference in information processing required when the response is or is not to be given on the same side as the stimulus.

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A TRIAL BY TRIAL STUDY OF THE VISUAL OMISSION RESPONSE IN REACTION
TIME SITUATIONS

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INTRODUCTION

The present work was undertaken in order to study the mechanisms underlying the various stages of perceptive and perceptive-motor processes by analyzing the characteristics (latency, amplitude and topographical distribution) of its electrophysiological correlates.

The brain response to a relevant stimulus which delivers information the subject has to process in order to perform a task (in particular, a motor task) is quite a complex response made up of stimulus and motor related components (occurring usually during the first 200 msec), followed by slow components which are considered to be chiefly related to cognitive processes. These slow components include, in particular, the so-called P300 wave which is often preceded by a negative component, N200. N200 is difficult to analyze since it occurs (at least in the case of visual stimuli) at the same time as the P200 visual component. Indeed, this P200 component usually has so large an amplitude and so wide a topographical distribution on the scalp that not only does it hide N200 but since the scalp acts as a spatial averager, it sometimes also mingles with P300.

For the above reasons we have used in this study the "missing stimulus" paradigm requiring a motor response from the subject whenever the stimulus is omitted. This experimental situation is particularly suitable for studying the preparatory stage of perception; moreover, with such a paradigm the electrical correlates of perceptive-motor processes are not distorted by the stimulus-related potentials.

In a previous work dealing with the same missing stimulus paradigm in which either a motor task or a counting task was required of the subject in response to each missing stimulus (Renault et al., in press), two types of responses to omission were differentiated on the basis of spatio-temporal criteria: a "vertex type", in which both components (the negative and the positive) peaked at the vertex, and a parietal one. These topographical characteristics were related to the nature of the task required from the subject. The parietal type of omission response was significantly more frequent, and the parietal activity was of higher amplitude during the counting task. The vertex type was more frequently observed during the motor task. On the other hand, during the motor tasks, contrary to the positive waves which often appeared during or just after the motor act, the negative component always occurred before the motor act. The latency of the negative component was strongly correlated with the reaction time (RT). This last result suggested that the negative components could reflect a preparatory stage of decision depending upon sensorimotor processing, whereas the positive waves might be related more to the execution of the task. These assumptions were based on the high correlation observed between the latency of each component of the omission response and the reaction time (RT). In fact, such a high correlation between these two phenomena (omitted response and reaction time) is not necessarily the sign of causal relationships since they could both depend upon a third internal event, e.g., the subject's estimation of the moment the omission should have occurred.

Therefore, after having designed an experiment enabling evaluation of the accuracy of this "time estimation" of the subject, the present work was undertaken in order to shed some light on the nature of the internal events which determine response. This was achieved by analyzing the relationships between the "time estimation of the omission" and the various characteristics of the scalp recorded omission response, as well as those of the performance of the required task.

METHODOLOGY

Experimental Design

Seven normal adults (six right-handed and one left-handed) served as subjects for this study. The responses to omitted stimuli were obtained in situations during which 450 visual stimuli (appearance, in the center of a screen, of a 20° checkerboard for 22 msec) were delivered at a rate of one per second. Ten percent of the stimuli were randomly omitted. In order to minimize eye movements, subjects were asked to fixate the center of the screen.

Two different omission situations were tested. In the first situation subjects were asked to beat the rhythm (with the second finger of their preferred hand) at the same frequency as that of the visual stimuli; whenever the visual stimulus was missing they were required to give, as quickly as possible, an additional motor response (RT) with the same finger. The "beaten rhythm" was considered as an index of the subject's time estimation of the moment the stimulus should have occurred; its latency with respect to this moment was taken as a measure of the subject's accuracy of time estimation (ATE). In order to estimate the modifications introduced by the "beaten rhythm", a second situation was used in which subjects were only asked to give, as quickly as possible, a motor response after each omission. Both movements (beaten rhythm and RT movements) consisted of a finger displacement towards a photoelectric cell and thus required very little strength. This kind of movement was chosen in order to minimize scalp recorded potentials related to the motor act (Kutas and Donchin, 1977).

In addition, in order to study motor related potentials in absence of all other event related potentials, a third situation was recorded during which the subject was asked to perform self-paced finger displacements at approximately the same rate of one per second with any visual stimuli occurring.

Electrophysiological Recordings

Recordings were made with a montage of eight equally spaced electrodes (10% of the nasion-inion distance apart) extending from inion to Fz and thus including Oz, Pz and Ca. Electrodes were referred to linked ears. The time constant was 1.5 sec with an upper bandpass limit of 220 Hz. Horizontal and vertical electro-oculograms were recorded and every response occurring during or after an eye movement was suppressed from the analyzed data.

On-line analog-to-digital conversion was performed at a 500/sec sampling rate. The data were displayed off-line by computer (BGE Gamma M40) in form of chronograms and spatio-temporal maps (Remond, 1961). Spatio-temporal maps were obtained for each subject from single trial data following each missing stimulus as well as from averaged data. In this case for each subject the averaging process was triggered successively by the moment of occurrence, by that of the "beaten rhythm" and that of the motor response (RT) to the missing stimulus. Besides, all the single trial omission responses (45 per subject in each situation) were averaged across subjects, the time trigger for this averaging process being one of the peaks of the response.

Recognition Procedure in the Trial by Trial Study

For each subject, the missing stimulus response obtained from average spatio-temporal maps was utilized as a template in order to visually identify each component of each single trial response to omission. The single trial peaks were visually identified on each map prior to knowing the time of occurrence of each motor act (beaten rhythm and reaction time response). This visual analysis was performed within a time window extending from one second before an omission to one second after. The only responses taken into account were those for which the signal-to-noise ratio made it possible to measure the values of latency, amplitude and topography for each component.

RESULTS

Organization of the Single Trial Omission Responses

As seen on the average single trial maps obtained across subjects, in both situations (with and without the presence of a "beaten rhythm") the response to the missing stimulus was made up of a negative component beginning in the parieto-occipital region (Na) which peaked later towards the vertex (Nb) followed by two positive components, the first one peaking at the vertex (Pa) and the second one (Pb) peaking in the parieto-occipital region (Fig. 1). It must be noted that during both situations (with and without the beaten rhythm) the parieto-occipital activity began around the moment of the omission and lasted for 600 msec, whereas the central activity (Nb and Pa) began approximately 200 msec after the omission and stayed on for 250 msec (this vertex activity disappeared about 450 msec after the omission). A slow late negative wave was also seen peaking posterior to the central area. It followed in time the vertex positivity and ended approximately at the onset of the next visual stimulus.

In fact, such an organization of the omission response, including Na, Nb, Pa and Pb, was found in 76% of all single trial responses. The remaining 24% of responses could be distributed into three groups: the first one was composed of only one negative wave followed by one positive wave, both peaking at the vertex (13% of the cases); the second one was made up of two components both peaking in the parieto-occipital region (6%); the remaining 5% were made up of omission responses in which the peaks of the two negative waves (Na and Nb) were clearly differentiated, the first one peaking in the parieto-occipital region, the second one on the vertex, both of them followed by a positive wave peaking in the same region.

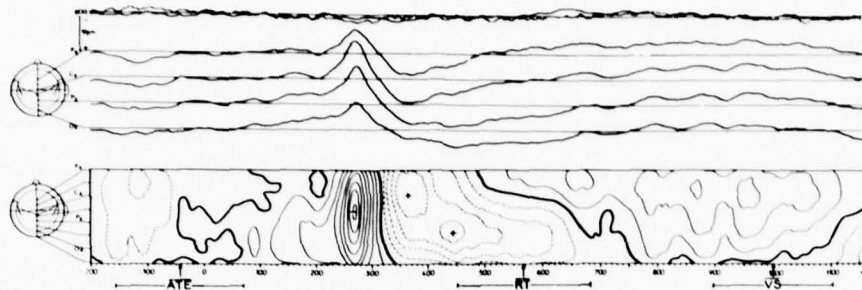


Fig. 1. Average of 165 single trial omission responses (across subjects) triggered by the negative vertex peak. Above, the data obtained from four derivations of the montage are represented in the form of chronograms. Average horizontal (broken line) and vertical (plain line) eye movements are superimposed in the upper traces. Below, the spatiotemporal map obtained from the whole montage. Amplitude is plotted in the form of isopotential lines as a function of time (in abscissa) and space (electrode location in ordinate); the values between two successive electrodes are obtained by interpolation. From one isopotential line to the next the difference of potential is equal to 1.6 μ V. Plain thick lines indicate potential 0; plain thin lines indicate negative potentials, broken lines positive potentials. The omission response extends from 50 to 650 msec; the exact location of the peaks is indicated by the sign - or + according to their polarity. The mean and standard deviation values of RTs, ATEs and moments of occurrence of the next visual stimuli (VS) are indicated in the abscissa.

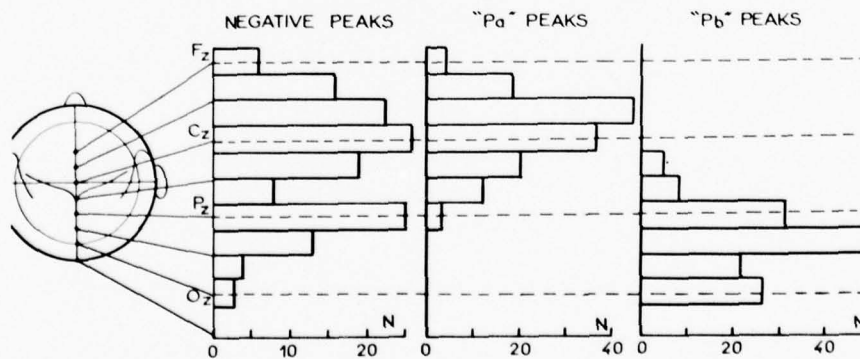


Fig. 2. Histograms of the peaks' locations obtained from the most typical type of omission response (76% of the cases, see text).

This spatio-temporal organization - in particular that illustrated by the single trial responses made up of four well differentiated peaks - suggests that two cortical regions play a role in the genesis of both the negative and positive components of the omission response: the parieto-occipital area for the negative Na and positive Pb waves, and the central area for the negative Nb and positive Pa waves. This assumption is supported by the topographical analysis of the most typical response to omission which has been described above (76% of the single trial responses, Fig. 1). Indeed as shown by the peak location histograms of their components (Fig. 2), the distribution of the positive components Pa and Pb differed quite significantly ($t = 30$, $p < .0001$); moreover the peak location histogram of the negative component appeared as bimodal, thus corroborating the existence of two active regions - a parietal and a central one - which might show the maximum of their activity either simultaneously or successively.

Average Scalp Potentials Related to the Motor Act

The spatiotemporal organization of the average potentials related to self-paced movement (third situation) was quite different from that of the omission response (Fig. 3). It mainly consisted of two successive waves, a negative one appearing before the movement (readiness potential) followed by a postmotor wave. Both these motor related components peaked more anteriorly than did the omission response in the fronto-central region. As it could be expected on account of the nature of the required movements, their amplitudes were quite small (less than 3 μV) compared to the amplitudes of the components of the omission response which all had a mean value of approximately 20 μV (Table I).

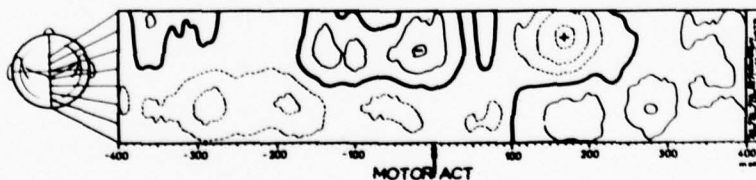


Fig. 3. Averaged motor related potentials obtained during the self-paced movement situation (seven subjects, eighty motor acts per subject). On the time scale, 0 indicates the occurrence of the actogram which triggered the average process. Between two successive isopotential lines the difference of potential is equal to .8 μV .

Table 1. Characteristics of the peaks of the omission response (average of each trial across subjects). ATE and latencies (L) are measured in msec with respect to the instant of the omission; topographies (T) are measured in % of the nasion-inion distance with respect to the inion; amplitudes (A) are measured in μV with respect to the baseline.

		Negative Peak			Pa "Vertex"			Pb "Parietal"			RT	ATE	N
		Lmsec	A μV	T%	Lmsec	A μV	T%	Lmsec	A μV	T%	msec	msec	
Situation 1	S	265	19.5	42	383	22	55	508	20	22	568	742	165
	S.d.	101	8.4	14	104	9.6	10	114	9.7	8.3	113	110	
Situation 2	S	274	21	39	386	21	52	507	18	23	503	/	140
	S.d.	115	10	11	107	8.6	8.4	106	7.3	10	127		

Time Relations Between Omission Responses, "Beaten Rhythms" and RTs

For each situation (with and without beaten rhythm) Table I depicts the mean characteristics (obtained across subjects) of the single trial omission responses, RTs and ATEs. It must be noted that the latencies of the components of the omission response did not significantly vary across the two situations (with and without beaten rhythm), whereas RTs were significantly longer in the beaten rhythm situation ($t = 4.54$, $p < .001$). As the duration of the movement is approximately 60 msec, this RT lengthening must be due to a mechanical inertia phenomenon since the beaten rhythm and the motor act are performed by the same finger.

As seen in Table II, all components of the omission response always occurred after the beaten rhythm. Concerning the RT response, the negative components always occurred before the motor reaction time response, whereas Pa could peak just after the motor act in some cases (10%), and Pb either just before or a long time after this motor act. The large range of variation of the RTs with respect to the latency of the peaks of the omission response must be noticed (Table II).

However, in both missing stimuli situations the latencies of the different waves of the omission response were strongly and positively correlated with the RTs, whereas their correlations with ATEs were much lower (Fig. 4). Moreover, ATEs and RTs were weakly correlated ($r = .35$). Thus the variability of ATEs cannot explain either the variability of the latencies of the omission response or that of the RTs, and consequently those two latter variables (RTs and ATEs) do not depend on each other.

This absence of correlation between ATE and RT prompted us

Table II. Time relations between peaks of the omission response, RTs and ATEs.

		SITUATION 1			SITUATION 2		
		Negative Peak	Fa "Vertex"	Fb "Parietal"	Negative Peak	Fa "Vertex"	Fb "Parietal"
Time occurrence	min. max	-592 ; -152	-468 ; 20	-320 ; 124	-580 ; -102	-440 ; 56	-318 ; 112
/ RT	\bar{x}	-304	-186	-60	-229	-116	4
(msec)	s.d.	98	96	99	81	79	87
Time occurrence	min. max	68 ; 714	168 ; 838	260 ; 968			
/ ATE	\bar{x}	307	425	550			
(msec)	s.d.	130	133	143			
Peak latency							
and RT correlation		.62	.61	.56	.66	.64	.59
Peak latency							
and ATE correlation		.23	.19	.14			

minus (-) indicates that the peak occurs before the RT.

to process our data in the following way in order to better understand the time relationships between these various events: Across subjects all single trial reaction times were divided into quartiles as a function of their duration, and the corresponding single trial omission responses were then averaged together as a function of the RT quartiles (Fig. 5). A significant relation was then found between the duration of RTs and that of the negative parietal wave. The longer the RT, the longer this wave lasted. The onset of this parietal wave was not correlated to the RT, nor was the duration of the other components. In addition, the increase in duration of the parietal negative component of these average omission responses was less important than that of the corresponding RT quartile (Fig. 5).

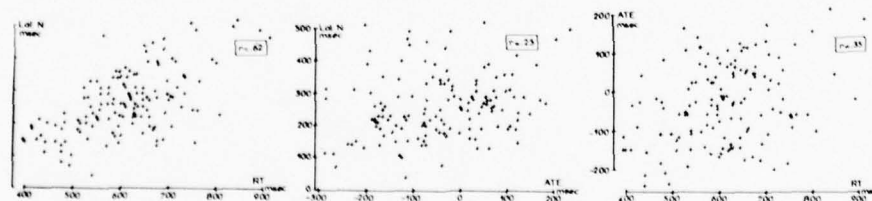


Fig. 4. Latencies of the negative peak of the omission response plotted against RTs (on the left) and against ATEs (in the middle); ATEs against RTs are plotted on the right. The corresponding coefficients of correlation are noted in a cartridge.

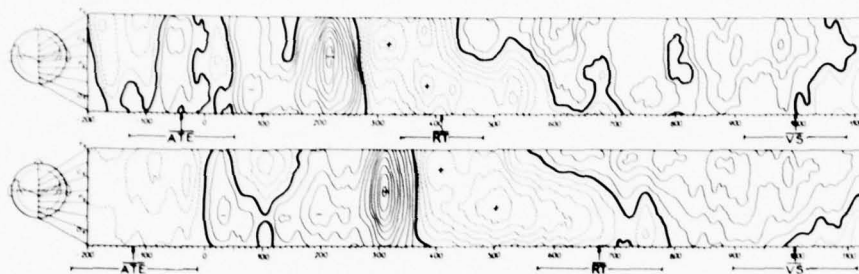


Fig. 5. Averaged spatio-temporal maps (across subjects) triggered by the negative peak of the omission response for the first RT quartile (above) and the fourth RT quartile (below). Between two successive isopotential lines the difference of potential is equal to 1.6 μ V.

DISCUSSION

Hypothetical Underlying Generators

The spatiotemporal organization of the omission response analyzed in the present study confirms the existence of two active cortical regions playing a role in the genesis of this potential: the parieto-occipital area and the central one, the former being active for a longer time than the latter. Since the scalp acts as a spatial averager, the activities from both generators (the parietal and the central one) most of the time add up, yielding a complex response which exhibits an apparent flowing of activity going from the parietal towards the central area for the negative components and from the central to the parieto-occipital region for the positive components.

These results confirm our previous findings concerning this omission response (Renault and Lesevre, in press; Renault et al., in press) as well as the existence of the two types of P300 (a central Pa and a parietal Pb) first reported by Squires et al. (1975). Moreover, they confirm the existence of negative waves preceding each P300, a vertex one (reported by Courchesne et al., 1976; Squires et al., 1977) and a long duration parietal one described by Simson et al. (1976).

This omission response was followed by a negative frontal potential of long duration (Figs. 1 and 5) which spread all over the scalp and lasted until the occurrence of the next visual stimulus. This late negative potential cannot be due to the

readiness potential related to the motor act (illustrated in Fig. 3) since its spatio-temporal organization is quite different and its amplitude much higher, and also because it still goes on a long time after the performance of the motor act. Squires et al. (1975) were the first to report the existence of a slow wave (S.W.) which was described as being negative at Fz, near zero at Cz and positive at Pz; our spatiotemporal data (Figs. 1 and 5) suggest that, in fact, the negative Fz and positive Pz must probably represent two distinct phenomena, one (positive) ending in the parieto-occipital region when the other one (negative) is starting in the frontal region. The fact that this negative frontal activity lasts until the onset of the next expected visual stimulus is in favor of its probably being a CNV.

Omission Response and Timing of Perceptivo-Motor Processes

Concerning the time relationships between the various electrophysiological and behavioral events analyzed in the present study, the following results have emerged:

- a) The latency of each component of the omission response, i.e., of the parietal as well as the vertex peaks, was positively correlated with the RT but appeared to be independent of the subject's estimation of the moment the omission should occur, evaluated by the beaten rhythm. These findings are consistent with the assumption that all peaks of the omission response reflect decision-making, but not with the hypothesis that the time estimation of the moment the stimulus should appear represented the internal time trigger on which depends the spatiotemporal organization of the omission response.
- b) The increase of the latencies of all peaks of the omission response, which was observed when RTs increased, was, in fact, due to an increase of the duration of the first parietal wave and not to a delayed time estimation of the moment the stimulus should have occurred. This finding suggests that this parietal negative wave could reflect some stimulus evaluation process. The longer this process would last, the later the decision to respond would occur. Besides, it must be noted that several previous findings are consistent with the hypothesis that this negative component is chiefly related to stimulus characteristics, in particular its topography has been said to change according to sense modality (Simson et al., 1976), or in the case of missing visual stimuli, according to the position of the expected stimulus in the visual field (Renault and Lesevre, in press).
- c) Two other results of ours must be taken into account: on the one hand, the fact that the increase in RTs was always more important than that of the duration of the negative parietal wave,

and, on the other hand, that there were large variations of the time of occurrence of all peaks in respect to the occurrence of the motor act. These findings show the complexity of these time relationships and fit with the view developed by Kutas et al. (1977) regarding the existence of two concurrent processes initiated by task relevant stimuli, i.e., a stimulus evaluation process, which would be reflected in our data by the duration of the negative parietal wave, and a response selection process. In addition, our results suggest that the vertex peaks (Nb-Pa) could index the "coupling" between these two parallel processes. Indeed, this coupling would produce some sort of a surprise effect (vertex response) which, in turn, would permit quickly giving an overt response whenever the selection response process is already over (quick RT cases) or starting this selection response process (slow RTs).

In conclusion, our results support the assumption that the negative parietal activity (Na wave) could reflect the stimulus evaluation time, whereas the vertex Nb-Pa waves would index the instant when the two above-mentioned parallel processes (the motor and the sensory one) get coupled. Therefore, the parietal positive activity (Pb) would last as long as the sensorimotor processing. It should be noted that in such a speculative model the time occurrence of the Pb wave with respect to the motor act would be an electrophysiological correlate, depending upon the "strategy" the subject uses during such complex motor RT tasks. This strategy can, indeed, favor either speed or accuracy of reaction (Kutas et al., 1977) or, in other words, either the motor or the sensory aspect of the task evaluation (Renault et al., in press). When speed or motor evaluation is emphasized, the motor act occurs before the parietal positive wave, and on the contrary, when accuracy or stimulus evaluation are emphasized the motor act then occurs after this Pb wave.

SUMMARY

This study was intended to explain the relations between event related potentials obtained in a missing stimulus paradigm and i) the estimation of the moment of occurrence of the missing stimulus; ii) the sensorimotor processes involved when the subject is asked to give a motor response after having detected the missing stimulus. These results support the assumption that two processes are initiated after the time estimation of the omission: a stimulus evaluation process reflected by the duration of the negative parietal wave and, concurrently, a response selection and execution process, indexed by the overt motor response. Moreover, it is assumed that the coupling between these two processes could be reflected by the vertex negative-positive potentials, whereas the relative timing

of the RT with respect to the parietal positive activity would be related to the strategy used by the subject.

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EVENT RELATED POTENTIAL RESEARCH IN PSYCHIATRY

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Over the last few years our laboratory has applied event related potential (ERP) techniques in three main research areas: psychopathology, normal aging and drugs of abuse. In this research we have used a variety of paradigms eliciting a variety of ERP components. It is a matter of efficiency to administer a battery of paradigms to subjects from populations that are difficult to select and recruit. The paradigms in a battery are chosen to elicit ERP components at various recording sites and latencies, and which reflect various stages and types of brain activity.

The sensory modality we have used has been primarily auditory. Our subjects sit in a sound attenuated chamber and hear clicks, noise bursts or shaped tone bursts. Depending on the paradigm, brain stem potentials, middle latency and auditory evoked potentials (P1, N1, P2) or the sustained potential (SP) are elicited. Under the proper task conditions the potentials representing cognitive processes more remote from sensation are elicited: P3, or the late positive wave, the CNV and the slow wave. The sensitivity of a component to the clinical phenomena under study depends on the precise conditions under which the component is elicited. Important sensory parameters are intensity and interstimulus interval (ISI). Cognitive parameters are as varied as the scope of the word cognition. We have used target detection tasks, dichotic selective attention tasks and memory retrieval tasks, as well as non-task paradigms.

SCHIZOPHRENIA

Our research in schizophrenia encompasses three studies. The

first compared twenty-one schizophrenics at St. Elizabeths Hospital with twenty-one age-matched controls (Roth and Cannon, 1972). Subjects were exposed to non-task relevant sequences of tones and noise bursts at about 70 dB sound pressure level (SPL). The noise bursts occurred randomly with a probability of 1/15 and elicited a positive wave at about 220 msec which was prominent in control subjects for the first twenty presentations of the noise bursts. In retrospect this wave is probably a composite of P2 and P3 components. Schizophrenics generally showed no such wave. Only seven of forty-two subjects were misclassified when a criterion voltage of 3.2 μ V was set for P3 amplitude to the first ten stimuli.

We explored this positive wave in a series of experiments (Roth, 1973; Ford et al., 1973, 1976a, 1976b) and, after developing a paradigm that we thought would elicit a reliable P3 in passive subjects (Roth et al., 1976a), we did a second study comparing schizophrenics and controls (Roth et al., 1978a). Subjects were twenty-five schizophrenics meeting the Research Diagnostic Criteria (RDC) from a Veterans Administration Hospital and twenty age-matched controls. Over one-third of the patients were drug-free. The stimulus eliciting P3 was an 80 dB SPL noise burst that occurred randomly in a sequence of background 65 dB SPL 800 c/sec tone pips. Half of the noise bursts were immediately preceded by a 1200 c/sec tone pip which served as warning. The probability of the warning tone and the unwarned noise burst were both 0.1, and both elicited P3s. Unfortunately this paradigm failed to show significant P3 differences between our schizophrenics and controls. Although mean values of P3 were more than 2.5 times larger in controls, there was much overlap of P3 amplitude between the two populations. The chief problem appears to be that some controls produced negligible P3s, while others produced large ones.

In addition to the P3 paradigm, two other paradigms were included in this test battery: a CNV paradigm and a tone-intervals (recovery function) paradigm. The CNV was elicited by a warning tone (S1) followed 1 sec later by a series of light flashes (S2) to which subjects pressed a button as quickly as possible. The intertrial intervals were 33-58 sec since we wanted to be sure that CNV resolution was complete by the time a new trial was started. The EEG amplifiers were set to have a time constant of 10 sec. Electrodermal activity was eliminated by using pin electrodes. Averages were computed from 5.5 sec epochs of EEG which had been edited for various artifacts. Eye blinks were compensated for by a subtraction procedure. Fig. 1 shows grand averages for 3.5 sec of the epoch. Although at Cz the CNV appears to remain more negative after S2 for the schizophrenics than for controls, this difference is not significant. We considered this failure to replicate the results of Timsit-Berthier et al. (1973) and the Montreal group (Dobrovsky and Doncier, 1976) possibly to be due to differences in the kinds of patients tested. The Montreal group found the most

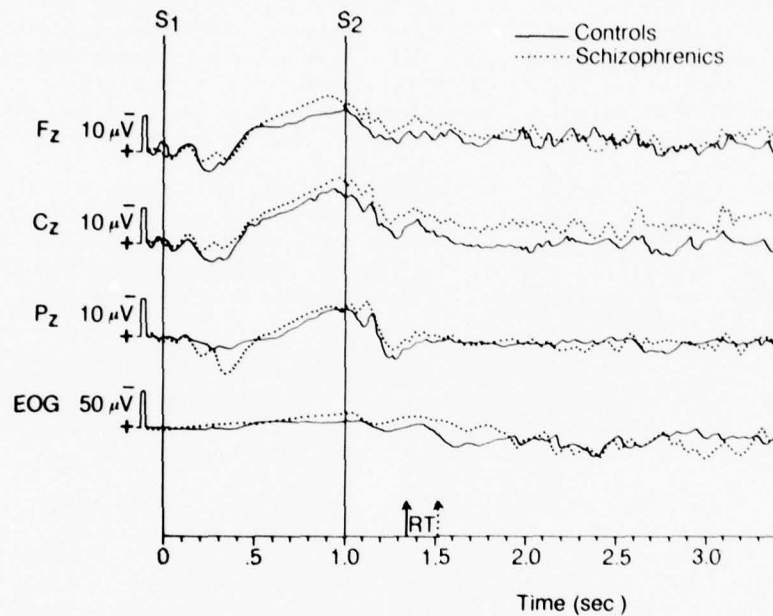


Fig. 1. ERPs for controls and schizophrenics combined across all subjects. The averages are comprised of about eleven trials/subject X 25 subjects. S1 marks the warning tone and S2 the onset of the imperative light flashes. The arrows on the abscissa indicate mean RTs.

striking prolongation in patients who had been ill for less than six months, whereas almost all our patients had been ill for more than a year. In general our patients' illnesses, although chronic, had not required continuous hospitalization.

The tone-intervals paradigm delivered 65 dB SPL 50-msec tone pips at ISIs of 0.75, 1.5 and 3.0 sec in a random sequence. The amplitudes of N1 and P2 varied with ISI, as we knew they would (Roth et al., 1976b), but there were no differences between schizophrenics and controls. Differences in temporal recovery had been shown previously for earlier peaks using somatosensory (e.g., Shagass, 1972)

and visual stimuli (Floris et al., 1968; Speck et al., 1966).

Our third and most recent study of fifteen schizophrenics and fifteen age-matched controls used a modified and expanded test battery of six paradigms, the first three of which were under the direction of Dr. Pfefferbaum. About half of the patients had been free of medication for at least two weeks prior to testing. In all except the last paradigm the subjects were given no task but asked to sit quietly. Briefly, the paradigms were as follows:

1. Click intensities: Clicks were delivered every 40 msec at 60, 70, 80 or 90 dB above an individual's sensation level (SL) threshold in random order. Averages of 2048 trials were computed for a 10 msec epoch. Fig. 2 illustrates sample waveforms for this paradigm. The amplitude and latency of wave V of the brain stem potential were measured.

2. Click intervals: 2048 90 dB SL clicks were delivered with an ISI of 20 msec, followed immediately by a series of identical stimuli delivered at an ISI increased to 80 msec. Wave V was measured as in the first paradigm.

3. Tone intensities: 500 c/sec tones 480 msec long were delivered with an ISI of 1.5 sec from tone onset to tone onset. Tone intensities were 50, 60, 70 or 80 dB SL presented in random order. Averages were computed for 64 trials of each intensity. Fig. 2 illustrates the N1, P2 and sustained potential (SP) components of a typical normal subject. The amplitudes and latencies of these components were measured.

4. Tone intervals: 1000 c/sec 50 msec tones were given at 85 dB sound pressure level (SPL). Tones occurred at ISIs of 0.75, 2.25 or 6.75 sec in random order. Averages were computed for forty trials of stimuli preceded by each ISI. Fig. 2 illustrates the N1 and P2 peaks elicited in this paradigm. The amplitudes and latencies of these components were measured. N1 and P2 were much smaller after ISIs of 0.75 sec than after ISIs of 6.75 sec.

5. Noise tone: Four types of stimuli, each 1 sec in duration with an ISI of 4 sec from stimulus onset to onset, were delivered in random order. Stimuli were either 1000 c/sec tones or white noise and were either 100 dB SPL or 70 dB SPL. Averages were computed for forty stimuli of each type. N1, P2, P3 and SP were elicited. All components were measured in all conditions. P3 was most prominent in the EP to the 100 dB noise bursts.

6. Reaction time: 85 dB SPL 50 msec tones were given with a 1 sec ISI. Tones were 800 or 1200 c/sec. The sequential probabilities were 0.85 for the 800 or 1200 c/sec tone and 0.15 for the 1200 c/sec tone. Hence the former tones are referred to as "fre-

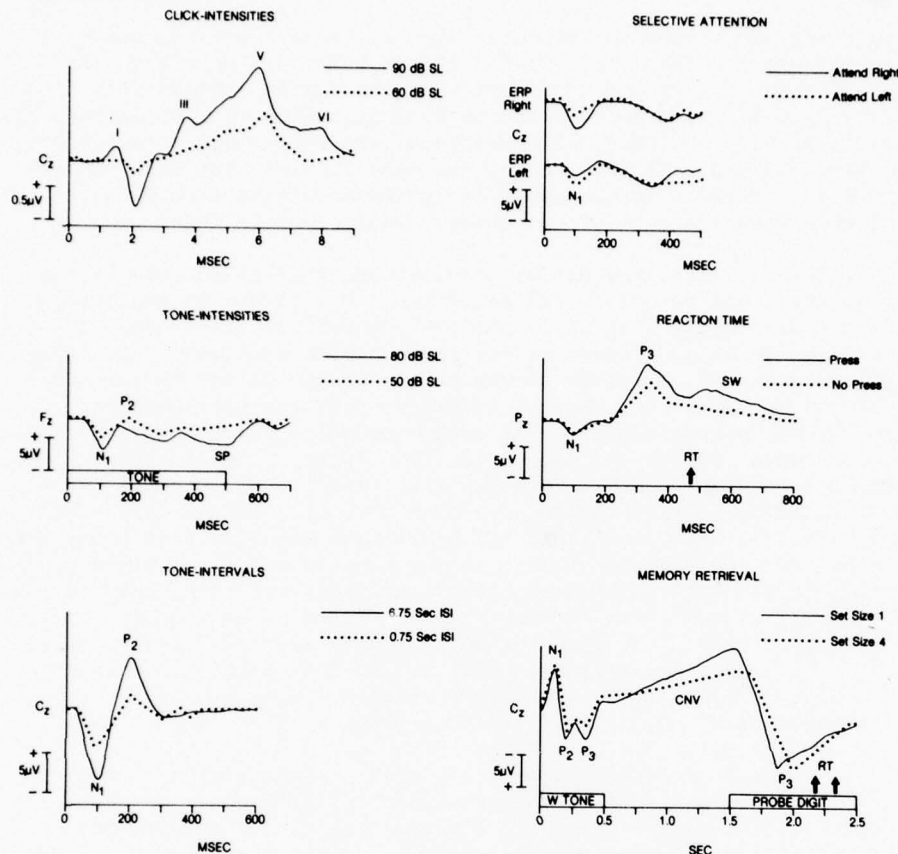


Fig. 2. Sample ERPs from six paradigms described in the text.

quents" and the latter as "infrequents". Subjects were instructed to press a button as quickly as possible upon hearing an infrequent tone. Averages were computed for seventy-five infrequent tones and 430 frequent tones. The frequent tones elicit N1 and P2; the infrequent, N1, P2, P3 and a slow wave (SW) (illustrated in Fig. 2). Amplitudes of all these peaks and latencies of all but the SW were measured.

The click-intensities and click-intervals paradigms showed the well known decrease in wave V latency as click intensity increased or as ISI became longer, but there were no differences between schizophrenics and controls. The tone-intensities paradigm showed complex effects depending on lead and intensity. In general, P2 was smaller and later in controls, and SP was greater. Larger P2s in schizophrenics were possibly due to a lack of the SP negativity

in their ERPs. The tone-intervals paradigm gave smaller N1s for schizophrenics than for controls at the 6.75 sec ISI but not at shorter intervals. Our hypothesis had been that endogenous auditory stimuli might be experienced by schizophrenics who, in general, are liable to auditory hallucinations, and this would effectively reduce the ISI. If this is so, our data implies that such endogenous interference in the auditory system manifests itself most clearly when the rate of exogenous stimulations is decreased.

The most striking differences between the groups were in the noise-tone and reaction time paradigms. N1, P2 and P3 amplitudes were considerably smaller in the schizophrenics, the P2 and P3 differences being largest in the 100 dB noise condition. Considerable startle blink reflex contaminated N1, but P2 and P3 were too late to be affected. The reaction time task was performed more poorly by schizophrenics. RTs were considered valid if they occurred between 100 and 600 msec after the targets. Schizophrenics made fewer responses within these limits (51 ± 22) than controls (68 ± 10). Schizophrenics were slower when they did respond (329 ± 51 vs. 283 ± 43 msec) and their RTs had larger standard deviations within an individual subject (70 ± 22 vs. 51 ± 13 msec). The amplitudes of P3 to the infrequent was considerably smaller in schizophrenics, while N1, P2 and SW to the infrequent showed no such effects. The latency of P3 was the same for both groups (mean 320 msec at Cz). The main difference between the groups in the evoked potentials to frequent stimuli lay in P2 latency which had a mean of 18 msec for schizophrenics and 217 msec for controls.

Stepwise discriminant analysis of the eight best variables as determined by analysis of variance selected P2 latency to the frequent as the best variable to discriminate schizophrenics from controls. It classified 13/14 controls correctly but only 7/12 schizophrenics. The next variable entered was P3 amplitude to the infrequent, but this did not improve the classification. When the P2 latency variable was excluded the first two variables picked were P3 amplitude to infrequent and N1 amplitude after the 6.75 sec ISI. These two variables correctly classified 11/14 controls and 9/12 schizophrenics. P3 and N1 amplitude to the 100 dB noise also had high F s-to-enter, but these variables correlated with the variables chosen and, hence, were not themselves chosen.

The combination of small P3s and more variable RTs suggests that perhaps latency variability of P3 in individual trials led to reduced amplitudes in a stimulus-synchronized average. Kutas et al. (1977) found P3 latency to vary with RT by analyzing their data with the adaptive filter invented by Woody (1967). We applied this filter to the P3 to infrequent and found that P3 amplitude increased more in schizophrenics than in controls after application of the filter but that schizophrenics still had significantly smaller P3s. Furthermore response-synchronized averages showed just as

great a P3 difference between groups as did the original stimulus-synchronized average. These results imply that latency variability does not completely explain the P3 amplitude differences and, in fact, the greater gain in schizophrenics' P3 amplitudes with the adaptive filter may be due to more noise in the schizophrenics' EEG.

Diminished P3s in schizophrenics has been reported from other laboratories (Levit et al., 1973; Shagass et al., 1977, 1978; Verleger and Cohen, 1978). The Bleulerian characteristic of schizophrenic autism would be expected to result in small or absent P3s since P3 amplitude depends on information being taken in from the external environment (Ruchkin and Sutton, 1978). Either schizophrenics fail to perceive that information is being delivered such as might occur if their subjective probability estimates were faulty, or they fail to react to such information in the same way as they tend to lack orienting responses.

NORMAL AGING

One of the greatest problems in doing research in aging is that with age comes disease. Diagnosed or undiagnosed disease can cause performance deficits that should be attributed to more specific pathological processes than the more general variable of age. In the study conducted under the direction of Dr. J.M. Ford, we recruited women older than 70 years who were subjectively and by history and physical examination in good health. None had active symptoms of cardiovascular, neurological, respiratory, renal, gastrointestinal or endocrine disease. Audiometry excluded subjects with sensation levels above 30 dB SPL at 500 c/sec. Thirteen elderly women between 74 and 87 years (mean (80.2) were compared with thirteen similarly healthy women between 20 and 29 years (mean 22.9). The mean raw IQ scores on the Wechsler Adult Intelligence Scale (WAIS) was 109 for the old and 145 for the young. If age adjusted, these scores would be 124 for the old and 121 for the young women. Mean years of education were 16.6 for the old and 15.8 for the young.

These subjects were tested on a battery that included the following paradigms:

(1) Tone intensities: As described above.

(2) Selective attention: This paradigm was based on the work of Hillyard and his students (Hillyard et al., 1973; Schwent et al., 1976a; Schwent et al., 1976b). Thirty dB SL 50 msec tone pips were presented at ISIs varying from 200-800 msec. Tones presented to the right ear were 800 or 840 c/sec presented randomly in a ratio of 10:1, and to the left ear 1500 or 1560 c/sec presented randomly in the same ratio. Subjects listened to the sequence of tones twice, once counting infrequent stimuli in the right ear and once counting

infrequent stimuli in the left ear. Fig. 2 shows sample waveforms for this paradigm for frequent stimuli in attended and nonattended ears. Amplitude and latency of N1 were analyzed in averages of 400 frequent trials for a given ear. P3 was measured for averages of 40 trials of the infrequent stimulus.

(3) Memory retrieval: This paradigm uses the task developed by Sternberg (1966) to measure the speed of retrieval of items from short-term memory. The ERPs that accompany normal performance of this task had been investigated in our laboratory previously (Roth et al., 1975; Roth et al., 1977; Roth et al., 1978b). Target and probe stimuli were the digits 0-9 presented for 1 sec on an oscilloscope. In each trial 1 to 4 target digits were presented consecutively with a 1 sec interval between them. The digits define a memory set with 1, 2, 3 or 4 members. One second after the memory set was ended a 0.5 sec warning tone (60 dB SL, 1000 c/sec) came on. One second after the warning tone went off the probe digit appeared. Subjects then pushed one of two telegraph keys to indicate if the probe was in or out of the memory set. Eight averages could be formed as defined by memory set size and whether the probe was in or out of the set. Each average was comprised of about twenty-two trials, only correct trials being included. Fig. 2 shows sample ERPs for in-set trials with set sizes of 1 and 4. N1, P2 and P3 to the warning tone were measured as were the CNV prior to, and the P3 following the probe. The last peak was located by computer as the maximum positive peak between 200 and 800 msec.

Old and young women differed on all three paradigms. The most striking finding from the tone-intensities paradigm was that the SP was much smaller in old than young ($p < .001$) in an analysis of variance with Fz, Cz and Pz). N1 amplitude was the same in both groups, P1 amplitude was larger in the elderly and P2 amplitude increased with intensity for the young but decreased or did not change with intensity for the old. This combination of findings cannot be explained by a nonspecific decrease in ERP amplitude with age. Pfefferbaum et al. (1978a) speculated that the SP decline in these old subjects corresponds to the loss of dendritic mass in the prefrontal cortex of aged brains that can be observed histopathologically.

The selective attention paradigm showed an N1 effect that was not statistically different in young and old subjects. This was true even though the counting of targets was less accurate in the old. P3 to the targets was significantly later in old (482 msec) than in young (402 msec) subjects [$F(1,22) = 11.70$; $p < .01$]. Ford et al. (1978a) took this as an indication that the cognitive deficit of old subjects in this task was not an attentional deficit but a slowness in reacting to relevant information.

The memory retrieval paradigm yielded a wealth of ERP and

behavioral data. RT was a linear function of memory set size for both in-set and out-of-set probes. According to Sternberg's model, the intercept of this function represents the sum of time to encode the probe and the time to make the motor response. The slope of this function represents the time to scan memory for a single digit. In our subjects the RT slope was greater in old (55 msec/digit) than in young (35 msec/digit) as had been reported previously (Anders and Fozard, 1973). RT intercepts were also greater in old (1028 msec) than young (720 msec). The latency of P3 to the probe did not follow the same pattern, however. The table in Ford's abstract in this volume lists these data. P3 latencies did increase with set size, but the slope of this increase was the same for young (27 msec/digit) and old (29 msec/digit). The intercepts were larger for old (448 msec) than young (369 msec) but were in both cases much shorter than RT intercepts. Dr. Ford postulated (Ford et al., 1978b) that P3 latency intercept represents encoding time and that the intercept of the difference between RT and P3 latency is a measure of motor time alone. If motor time were constant for each set size the slope of the RT-P3 latency vs. set size would be zero. In fact, the slope of this function is 46 msec/digits for old and 14 msec/digits for young. This greater gap between P3 and RT for greater set sizes in the elderly may represent a slowness in responding after a more difficult decision. Subjects are less confident of their decision when the memory set is larger. There were more errors when memory sets were larger which complicates interpretations of the dissociation between P3 latency and RT as being a manifestation of different speed vs. accuracy trade-offs (Kutas et al., 1977). For smaller set sizes there was both more accuracy and less dissociation, but task difficulty was less as well.

In summary, our general conclusions from this study were that old subjects moved much more slowly than young, encoded somewhat more slowly, scanned memory at the same speed but were considerably less confident about more difficult decisions.

PSYCHOACTIVE DRUGS

A number of psychoactive substances have been investigated in our laboratory using versions of the paradigms described above. Roth et al. (1977) tested the effects of marijuana and ethanol with this memory-retrieval paradigm, Hink et al. (1978) tested the effects of methylphenidate on a selective attention task and Pfefferbaum et al. (1978b) tested the effects of ethanol and meperidine with the tone-intensities paradigm. A version of the RT paradigm has been used both to test for acute effects of ethanol (Roth et al., in prep.) and to try to distinguish abstinent chronic alcoholics from controls (Pfefferbaum et al., 1978c). This version of the RT paradigm delivers three pitches of tone in random order. One pitch occurs frequently and two pitches infrequently. One of the infre-

quent pitches is the target for a button press and the other is not. The properties of this paradigm have been explored in normals (Roth et al., 1978c).

In the Pfefferbaum study ten chronic alcoholics and ten age- and sex-matched controls were tested. Alcoholics had a ten year or more history of drinking and met the Research Diagnostic Criteria for alcoholism. Subjects with neurological disease were excluded. All subjects had been abstinent from alcohol for at least two weeks and off psychotropic medications for at least one week at the time of testing. RTs were not significantly different between alcoholics (289 msec) and controls (272 msec). Neither were there significant P3 amplitude differences between groups for either target or nontarget infrequents. P3 latencies for targets were also comparable for the two groups, but the latencies of P3 to nontargets were less than 400 msec in all controls and greater than 400 msec in all of the alcoholics. This P3 latency measure was more sensitive than the Halstead-Reitan battery in distinguishing the groups: only three of the alcoholics had "definite" cognitive abnormality while one other was classified as "borderline". We have no ready explanation for these unexpected findings. In dementia, P3 latency is greater (Goodin et al., 1978), but why is latency greater only for nontarget P3s? We plan to continue these investigations and hope to ascertain among other things if this difference is irreversible or if it disappears after a longer period of abstinence.

RESEARCH GOALS

The main clinical use of electricity in psychiatry today is electroconvulsive therapy. Electrodiagnosis has not yet reached the point of usefulness. Yet our results indicate that ERP measures may be sensitive enough to distinguish schizophrenics from controls to a clinically useful extent. Now the specificity of these measures must be established. Would patients with affective disorders show similar changes? Since affective disorders are treated with medications different from those used in schizophrenia, distinguishing between the two is of practical importance. For ERPs to be useful they must be more accurate or more inexpensive than other methods for deciding which treatment a patient should receive, or evaluating the effectiveness of that treatment. Theoretical insights about cognitive peculiarities of schizophrenics that might be gained through ERP research are of much less interest to the clinician.

Studies of aging have different goals since there is little hope of reversing the nonspecific aging process with a particular treatment. Deviations from normal aging, however, may indicate the presence of specific and treatable disease, and so understanding of normal aging can provide a baseline for abnormality. Although another averaging technique, computerized axial tomography, can

tell us about structural alterations in the brain, more subtle functional alterations are more likely to show up with ERP testing. We plan to test this idea by using both methods in a new group of elderly people.

The acute effects of psychoactive drugs can be tested in a research design in which the subject is his own control. This is especially advantageous when measuring components that are very variable between individuals. ERPs can be the best indication that a drug is affecting the brain since biochemical evidences of drug effects require more invasive techniques. The difficulty with human ERP studies is that the establishment of dose-response and time-action curves requires many data points, each comprised of many trials. Unless such curves are established it is impossible to know whether differences between drugs are qualitative or quantitative differences. Chronic effects of psychoactive substances have not been the subject of ERP research previously because of the belief that ERPs had no particular advantage over other forms of cognitive testing. Now it is apparent that ERPs supplement RT and other measures of psychological function in an important way.

SUMMARY

Our laboratory has applied event related potential (ERP) techniques in three main clinical areas: psychopathology, normal aging and drugs of abuse. For the sake of efficiency, multiple paradigms have been administered to a single group of subjects. We recently compared schizophrenics and controls using paradigms that elicit auditory short (brain stem), middle and long latency potentials. Certain middle and long latency potentials differed markedly in latency or amplitude between the groups. In another study we compared healthy elderly women with healthy young women using a test battery that included a dichotic listening task and a Sternberg memory retrieval task. The pattern of ERPs elicited during these challenging tasks helped delineate specific cognitive deficits associated with aging. Several of our paradigms have also been sensitive to acute and chronic effects of psychoactive substances. In certain cases, our ERP findings apparently provide information about the human brain that cannot be obtained by other methods. Such unique information is the final justification for using ERP techniques in clinical areas.

ACKNOWLEDGEMENTS

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SPATIAL DISTRIBUTION OF SENSORY EVOKED POTENTIALS IN PSYCHIATRIC
DISORDERS

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The topographic dimension has received little attention in evoked potential (EP) investigations of psychiatric patients. Although EPs have been recorded most often from a single lead derivation, some studies involving recordings from more than one site have yielded findings which suggest that the spatial distribution of EPs may be of psychiatric interest. For example, Rodin et al. (1968) in a study of visual evoked potentials (VEPs) observed that assessments of psychopathology in schizophrenics were more often correlated with right than with left hemisphere VEP characteristics. Perris (1974) found that amplitudes of VEPs from the left occiput were lower than those from the right in psychotic depressives while they were ill. Buchsbaum et al. (1977) reported that, in a rapidly cycling manic-depressive patient, a VEP wave was decreased in amplitude at the vertex and increased at the occiput with mania and conversely with depression. Such observations encourage further exploration of EP topography with respect to possible psychiatric correlates.

In recent years we have been using a comprehensive EP recording procedure which was designed to accomplish several purposes; a principal goal was to obtain information about topography in relation to psychiatric criteria. In this procedure recordings were made from fifteen locations, and four kinds of stimuli in three sensory modalities are presented in one experimental session. We have already reported a number of positive findings (Shagass et al., 1977, 1978; Roemer et al., 1978). These can be summarized as follows: 1) In overtly psychotic patients of both schizophrenic and affective type, events occurring more than 100 msec poststimulus were of lower than normal amplitude in EPs of all modalities and in most lead

locations. 2) EPs of nonpsychotic patients and schizophrenics of the latent subtype were not grossly different from normal. 3) Chronic schizophrenics (paranoid and undifferentiated) differed from those of other subtypes with respect to a negative somatosensory EP (SEP) peak occurring at 60 msec poststimulus (N60); N60 was more negative posteriorly in the chronic patients. 4) Schizophrenics of all subtypes showed less waveshape stability than normal in VEPs recorded from the left hemisphere.

We employed a completely objective, automatic computer technique to evaluate EP differences between groups (Shagass et al., 1977, 1978). Mean EPs were obtained for each group and t-tests were computed for consecutive corresponding data points; the t-values were displayed as displacements from a horizontal line when they were significant (Fig. 1). The drawback of this method is that it cannot distinguish between effects resulting from differences in amplitude and those due to latency differences. This drawback can be particularly important if one wishes to evaluate group differences in the topography of EP events since apparent reductions in amplitude of a peak can result when the latency varies between subjects. Consequently, although the automatic method has provided some interesting topographic results, as in the case of the N60 wave, we found it necessary to use a technique based on visual detection of peaks in order to obtain more interpretable information about spatial distribution. The possible problems resulting from the subjective aspects of detecting peaks visually were mitigated by the fact that the results provided by the objective automatic method were also available; when the findings yielded by the two methods converged, they could be accepted with confidence.

We present here the results obtained by comparing several groups of psychiatric patients and nonpatient control subjects with respect to the spatial distributions of somatosensory, visual and auditory EPs. The patients included schizophrenics of several subtypes, psychotic depressives and nonpsychotics with neuroses and personality disorders.

METHODS

As the basic recording procedures and the subject groups have been described in full elsewhere (Shagass et al., 1977, 1978; Roemer et al., 1978), only an outline will be given here.

Subjects

Data are presented for eighty-eight psychiatric inpatients and thirty-three paid volunteer nonpatients. These subjects were all of those from a larger pool who could be matched for age and sex to

LEFT MEDIAN NERVE STIMULUS

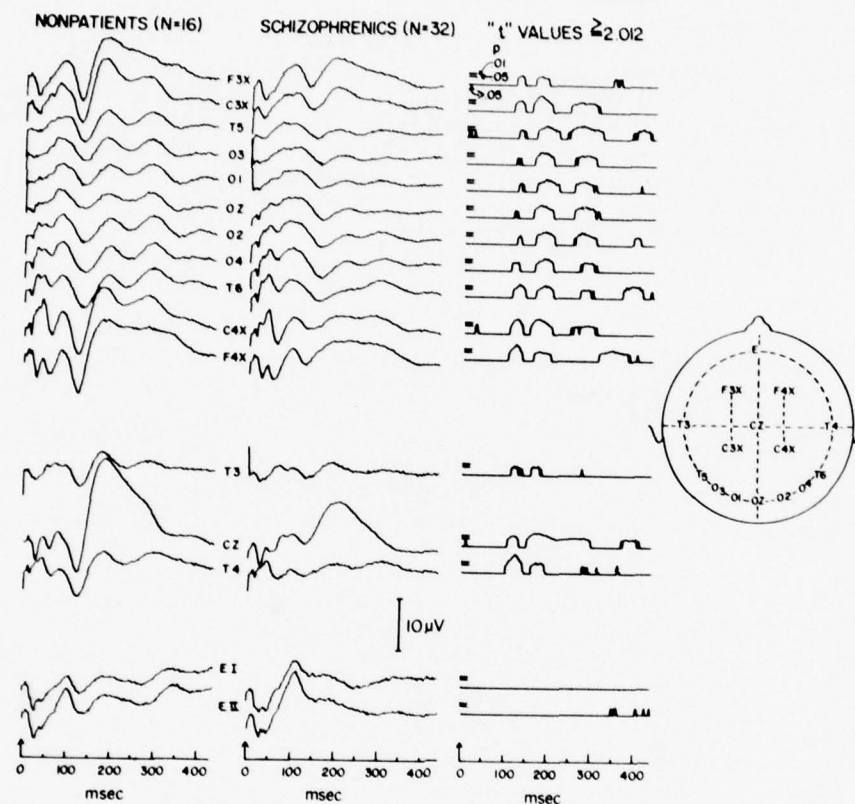


Fig. 1. Left and center columns: mean SEPs to left median nerve stimuli of sixteen nonpatients and thirty-two schizophrenic patients. All leads referenced to linked ears; scalp positivity gives upward deflection. Right column indicates results of 2-tailed t-tests performed on data points corresponding in time to those in EP tracings; t-values under 2.012 ($p=.05$) were kept at baseline in t-curve while values of 2.012 or greater were plotted according to magnitude starting at an arbitrary level above baseline (from Shagass et al., 1977).

provide the following comparisons: a) chronic schizophrenics ($N=26$) vs nonpsychotics ($N=26$) vs controls ($N=25$); there were nineteen men in the control group and twenty in each patient group; ages were about the same; b) latent schizophrenics vs "other" schizophrenics vs controls ($N=12$ each); c) psychotic depressives vs controls ($N=12$ each). Some controls were used in more than one comparison. Patients in the chronic schizophrenic group were subtyped as follows:

chronic undifferentiated, 14; chronic paranoid, 11; simple, 1. Subtypes included under "other" were: catatonic, 4; schizo-affective, 5; acute, 3. Latent schizophrenics conformed to criteria for pseudo-neurotic schizophrenia (Hoch and Polatin, 1949). Nonpsychotics included eleven neuroses and fifteen personality disorders. At time of testing, patients had been unmedicated for a median period of ten days. Diagnoses were made independently by at least two senior psychiatrists; excluding latent schizophrenia, 86% of the diagnoses met the relevant research diagnostic criteria of Feighner et al. (1972) to a definite or probable level.

Procedures

Recording leads are indicated in the head diagram of Fig. 1; the 10-20 system was followed with these exceptions: F3X, F4X, C3X and C4X were 2 cm posterior and 1 cm lateral to the standard position; O3 and O4, respectively, were midway between O1 and T5 and O2 and T6. Lead E was used to monitor EOG. All recordings were monopolar to the ears linked through a 22 Kohm resistor. Two montages were used; each included three pairs of homologous lateral leads, e.g., T3, T4, either Oz or Cz, and the EOG lead. Stimuli were: electrical pulses (0.1 msec duration, 10 ma above sensory threshold) applied percutaneously over left and right median nerves; a checkerboard pattern flashed briefly on a television (TV) screen; binaural auditory clicks 50 db above white noise level in earphones. Order and timing of stimuli was pseudo-randomized; mean interstimulus interval was 1.75 sec. There were 192 stimuli of each kind for each montage; averages (512 data points, 1 msec each) were summed on-line in a PDP-12 computer. Subjects sat fixating a spot on the TV screen.

Treatment of Data

Consecutive peaks were detected by visual inspection of selected leads for each type of EP, as displayed on the PDP-12 cathode ray tube. The leads were C4X and C3X for SEPs to left and right median nerve, respectively, Oz for VEPs, and Cz for auditory EPs (AEPs). A program was used to record time in the record at which a cursor spot was placed on a peak. Utilizing the convention of designating peaks by polarity and usual latency, the following peaks were detected: a) SEPs - P15, N18, P30, P45, N60, P90, N130, P185, P290; b) VEPs - N75, P90, N120, P200, P300; c) AEPs - P30, P50, N75, P90, N110, P180, P360. These peaks correspond well to those detected in group mean EPs of nonpatients (Shagass et al., 1977, 1978); Fig. 2 shows labelled examples of records in key leads. The latencies of these peaks in recordings derived from key leads were then used to make automatic measurements of amplitude at the same times in the records from all leads for EPs of a given type for each

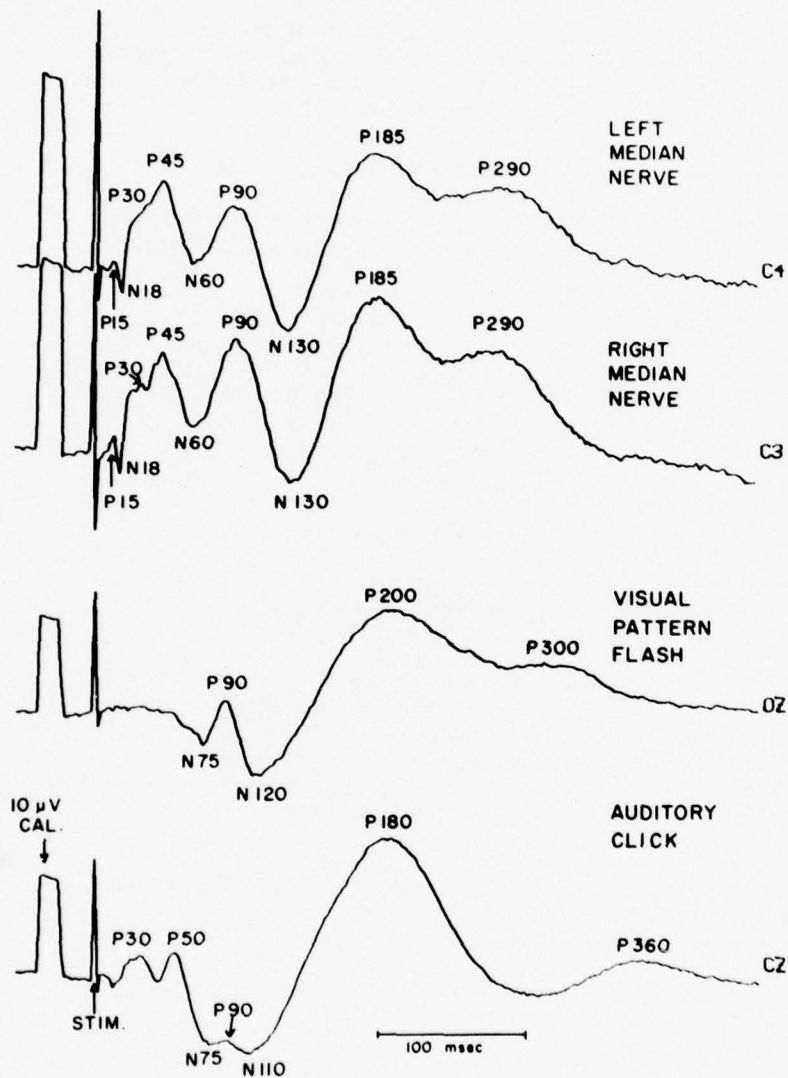


Fig. 2. EPs from key leads for visual detection of designated peaks; C4X (C4) for left median nerve SEP; C3X (C3) for right median nerve SEP; OZ for VEP; CZ for AEP. EPs are group means of twenty-five nonpatient subjects.

Table 1

SEPs - Left Median Nerve Stimulus
Results of Multivariate Profile Analyses Comparing
26 Chronic Schizophrenics (CS), 26 Nonpsychotics (NP)
and 25 Controls (C)

Peak	Mean Amplitude (μ V)					
	14 Leads			6 Contralateral Leads		
	CS	NP	C	CS	NP	C
P15	0.64	0.92	0.51	0.74	1.02	0.55
N18	-0.35	-0.36	-0.40	-0.78	-0.82	-0.75
P30	-0.03	0.52	0.14 _{a,d}	1.03	2.23	1.44 _{b,e}
P45	1.47	1.34	1.24 _d	3.08	2.52	2.47
N60	-0.11	0.58	0.42	-1.37	-0.16	-0.10 _a
P90	2.59	3.68	3.02 _d	2.35	4.23	3.31 _a
N130	0.29	-2.06	-2.42 _{b,d}	0.04	-2.22	-3.21 _c
P185	4.22	5.24	5.13	3.97	4.45	4.57
P290	2.26	3.76	3.85	2.61	4.05	3.86

a, b, c - p for means, respectively, < .05, < .01, < .001

d, e - p for diagnosis x lead interactions, respectively,
< .05, < .01

subject. A second version of the program allowed for latency variation by using the detected latency as the center of a time window extending 5% on either side; maxima or minima within this window were then detected for measurement. As results for the two procedures, i.e., absolute latency and + 5% variation, were very similar, only the absolute latency data will be presented here.

Amplitude measurements for a given peak across leads were subjected to multivariate profile analysis (Morrison, 1967). In this analysis differences between diagnostic groups in the spatial distribution of an EP peak would be reflected by a significant ($p = .05$) profile F-ratio, indicating a diagnosis by lead interaction. In addition, the analysis yielded F-ratios reflecting group differences in mean amplitude across leads.

RESULTS

Chronic Schizophrenics vs Nonpsychotics vs Controls

SEP. Multivariate profile analyses of the SEP data were performed in two ways: a) utilizing all fourteen scalp leads; b)

utilizing only the six leads on the hemisphere contralateral to the stimulated nerve, as the earlier SEP peaks are lateralized (Fig. 1). Table 1 summarizes the results for SEPs to left nerve stimuli. Mean amplitudes of P30 and N130 differed between groups across the fourteen leads; P30 amplitude was greater in the nonpsychotics than in the other groups, while N130 amplitude was lower in the chronic schizophrenics. The data for the six contralateral leads yielded mean amplitude differences for P30, N60, P90 and N130; P30 and P90 were highest in nonpsychotics; N60 was most and N130 least negative in chronic schizophrenics. Topographic differences between groups were indicated by significant diagnosis by lead interactions for P30, P45, P90 and N130 (fourteen leads); the six contralateral leads gave an interaction for P30.

Fig. 3 (right) shows the distribution of P30 and N60 amplitudes for five of the six contralateral leads (T4 was omitted because it is not aligned with the other leads). It will be seen that the highest amplitude of P30 was at lead O4 in the chronic schizophrenics, at T6 in the controls and at C4X in the nonpsychotics. The N60 distributions show about equal amplitudes for all three groups in the frontal lead; in the posterior leads negativity was greater in the chronic schizophrenics, being greatest at lead C4X. Fig. 4 displays distributions for P90 and N130; the T3, Cz, T4 leads are plotted separately because of their alignment in the coronal plane. P90

Table 2

SEPs - Right Median Nerve Stimulus
Results of Multivariate Profile Analyses Comparing
26 Chronic Schizophrenics (CS), 26 Nonpsychotics (NP)
and 25 Controls

Peak	14 Leads			6 Contralateral Leads		
	CS	NP	C	CS	NP	C
P15	0.76	0.69	0.64	0.94	0.88	0.84
N18	-0.55	-0.67	-0.36 _a	-0.83	-1.06	0.62 _a
P30	0.14	0.44	0.49	1.14	1.98	1.58 _d
P45	1.57	1.61	1.68	3.05	2.78	2.82
N60	0.29	1.46	1.57 _b	-1.01	0.47	1.01 _{c, d}
P90	3.69	4.94	4.30 _d	3.21	5.28	4.51 _{a, d}
N130	-0.10	-2.17	-2.36 _a	-0.42	-2.37	-2.66 _a
P185	3.42	5.82	5.52 _b	3.29	5.32	4.88 _{a, e}
P290	2.48	4.05	4.61 _{a, d}	2.50	4.35	4.40 _a

a, b, c - p for means, respectively, < .05, < .01, < .001

d, e - p for diagnosis x lead interactions, respectively, < .05, < .01

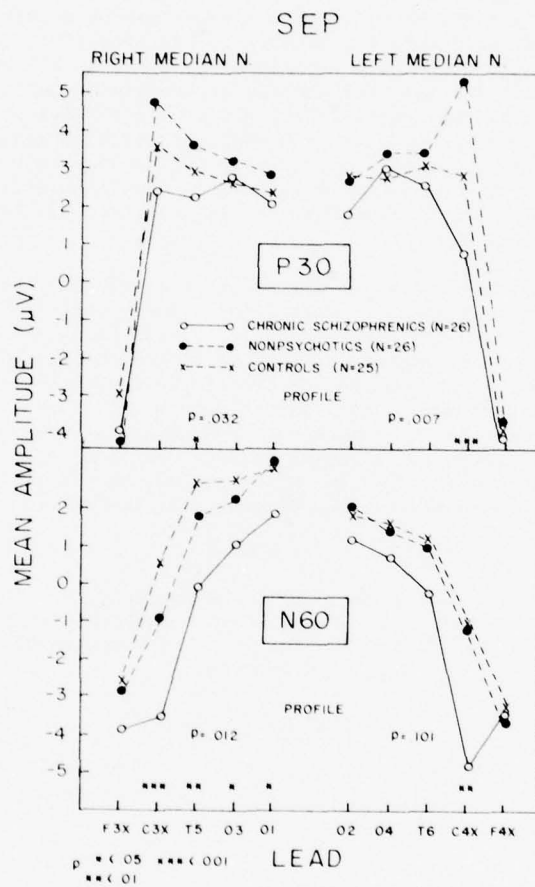


Fig. 3. Spatial distributions for chronic schizophrenics, nonpsychotics and controls of P30 and N60 in SEPs from hemispheres contralateral to stimulated nerves. Leads as in Fig. 1. Values for T3 and T4 not plotted. In this and subsequent figures asterisks indicate significant univariate F ratios; these are shown only when multivariate profile analysis was significant.

amplitude was greatest in the nonpsychotics in anterior leads, particularly in the right (contralateral) hemisphere. Chronic schizophrenics had the lowest P90 amplitude. The distributions for N130 clearly demonstrate the maximum negativity of this peak at leads around the vertex (Cz, C3X, F3X, C4X, F4X) for controls and nonpsychotics; in the schizophrenics there was very little negativity.

Table 2 summarizes the results for SEPs to right nerve stimuli. The groups differed with respect to mean amplitude for peaks N18, N60, N130, P185 and P290 in both sets of analyses; the data for the six contralateral leads showed an additional amplitude difference for P90. These amplitude findings indicate three trends: a) N18 was greater (more negative) in the nonpsychotics; b) N60 was more negative in the chronic schizophrenics; c) peaks from P90 on were of lower amplitude in the schizophrenics.

The profile analyses for right nerve SEP data indicated group differences in topography for P90 and P290 with fourteen leads and in P30, N60, P90 and P185 with only the contralateral leads. The left half of Fig. 3 shows the distributions for P30 and N60 in SEPs to right nerve stimuli; in general these are approximate mirror images of those obtained with left nerve SEPs. Maximum amplitude of P30 occurred more anteriorly in the SEPs of nonpsychotics than in those of schizophrenics. N60 peaks were more negative posteriorly in the schizophrenics than in other groups. Fig. 5 shows the distributions for peaks P90 and P290. As with the left nerve stimuli, P90 amplitude of nonpsychotics was greater in anterior leads and particularly on the contralateral side; also, although P90 amplitude of controls was like that of nonpsychotics in most leads it dropped to the level of the schizophrenics in the two frontal leads. P290 amplitude was greatest at vertex (Cz) in all groups and decreased more or less symmetrically with increasing distance from Cz. Controls had the highest and chronic schizophrenics the lowest P290 amplitudes. The significant interaction for P290 seems attributable to the variations between leads in the magnitude of differences between groups (Fig. 5).

VEP. Profile analysis of the VEP results yielded only one statistically significant finding; the distribution of P300 differed between groups. Fig. 6 (top) indicates the nature of the topographic differences. VEP P300 amplitude was greatest in controls in the coronal plane leads, particularly at Cz, while it was highest in nonpsychotics at most other leads; it was generally low in chronic schizophrenics.

AEP. Most of the significant AEP findings indicated group differences in mean amplitude. AEP peaks N75, P90 and N110 were generally less negative in the chronic schizophrenics, reflecting low amplitude of the component often designated as N1 which would include all three peaks. P180 was of greatest amplitude in the nonpsychotics.

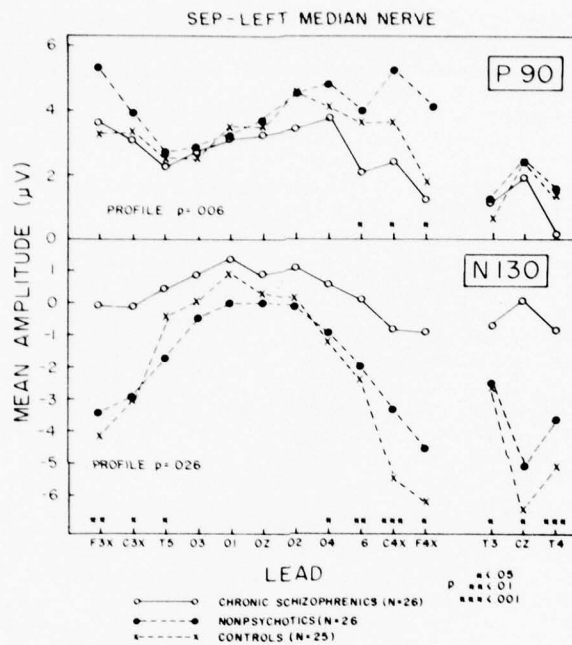


Fig. 4. Spatial distributions of peaks P90 and N130 in SEPs (left median nerve) of chronic schizophrenics, nonpsychotics and controls.

Topographic effects were demonstrated for P180 and P360. Fig. 6 (bottom) shows the P180 distributions; the amplitude of this peak was maximum at vertex in all groups and decreased symmetrically with distance from Cz. The topographic differences seemed to result from variations between leads in the magnitude of group differences. The P360 effect was of similar nature.

Latent Schizophrenics vs "Other" Schizophrenics vs Controls

Because the small number of subjects imposed constraints upon the number of variables that could be handled at once, the multivariate profile analyses for this set of comparisons were performed separately for the three coronal leads and the remaining eleven leads. The analyses involving eleven leads yielded only one significant difference; mean amplitude of peak P15 in the right nerve SEP was lower for the latent schizophrenics than for the other two groups.

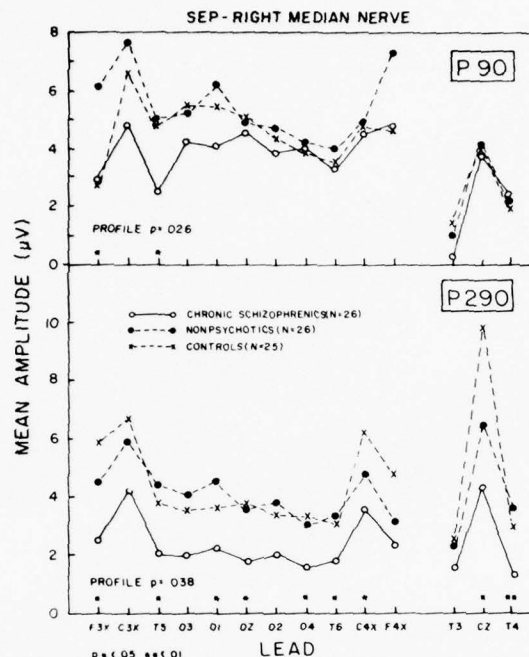


Fig. 5. Spatial distributions of peaks P90 and P290 in SEPs (right median nerve) of chronic schizophrenics, nonpsychotics and controls.

Eleven analyses involving the coronal leads yielded significant findings. For left nerve SEPs N18, P45, N60 and P290 differed between groups in mean amplitude; amplitudes of the "other" schizophrenics were lower than those of latent schizophrenics and controls for N18, N60 and P290 and higher for P45. P90 and P290 gave distribution differences that appeared to result from relatively low amplitudes at lead Cz in the "other" schizophrenics, while the group means were more similar at the T3 and T4 leads. For right nerve SEPs, mean P15 amplitude of the latent schizophrenics was relatively low, and mean P290 amplitude of the "other" schizophrenics was less than that of latents and controls. P15, P30 and P290 gave distribution effects and only that for P290 seemed clearly describable. As with left nerve SEP, it appeared to result from very low P290 amplitude at Cz in the "other" schizophrenics. The distributions of two VEP peaks (N75 and P200) and one AEP peak (P180) differed between groups. These effects could be attributed to greater negativity at Cz for VEP peak N75 in the "other" schizophrenics, greater positivity of VEP peak P200 at Cz in the latent

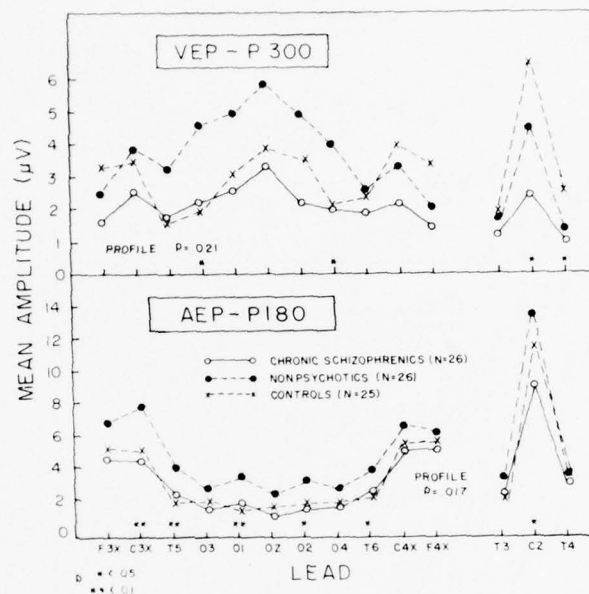


Fig. 6. Spatial distributions of VEP peak P300 and AEP peak P180 of chronic schizophrenics, nonpsychotics and controls.

schizophrenics and lower amplitude of AEP peak P180 at Cz in the "other" schizophrenics.

psychotic Depressives vs Controls

These analyses were also performed separately for the three coronal and the remaining eleven leads. The analyses involving eleven leads showed that the mean amplitudes of right nerve SEP peak P185 and AEP peak N110 were lower in depressives than in controls. Topography differences were found for right nerve SEP peak P290 and AEP peak P190. The SEP P290 effect seemed due to a reduction at T5 and T6 of the difference in amplitude at all other leads, that of controls being greater. For AEP P180 maximal amplitudes were more posterior in controls (at leads C3X and C4X) than in depressives (leads F3X and F4X). The analyses involving the three coronal leads yielded four group differences in mean amplitude - SEP N130 (both nerves), AEP P90 and N110 amplitudes were lower in psychotic depressives than in controls. An interaction for left nerve SEP peak N130 resulted from virtual absence of this peak in the depressives.

DISCUSSION

The data revealed a number of differences between the comparison groups with respect to both mean amplitudes of EP peaks and their spatial distributions. It seems pertinent to first consider the amplitude results because of their methodological relevance for the topography data. Convergence between the data yielded by the present method of detecting peaks visually and those provided by the previously used fully automatic technique (Shagass et al., 1977, 1978) would augment confidence in the reliability of the topographic data.

A main finding in our previous reports was that EPs of overtly psychotic patients differed from normal, particularly in events 100 msec or more poststimulus, while those of nonpsychotic patients and latent schizophrenics did not. Present results generally replicate this finding. In chronic schizophrenics amplitudes were lower than those of nonpsychotics or normals in SEP peaks P90 to P290 (Tables 1 and 2), VEP peak P300 and AEP peaks N75, P90, N110 and P180. Amplitudes of later EP events also tended to be lower in the group of "other" overt schizophrenics than in controls and latent schizophrenics and lower than normal in psychotic depressives. In addition previous evidence of greater SEP N60 amplitude in chronic schizophrenics was confirmed here (Tables 1 and 2). There was thus a degree of convergence between the results yielded by the two methods of measurement, allowing greater confidence in the topography findings than one might have if the automatically obtained data were not available.

SEP peaks P30 and N60 provided the topographic differences between clinical groups of greatest interest (Fig. 3). The P30 differences were surprising to us. Our impression from years of recording SEPs in all kinds of subjects was that P30 distribution was relatively constant, with maximum positivity at leads near the postcentral gyrus hand area (C3X, C4X). However, nearly all of our localization experience was with bipolar leads. While present data for nonpsychotic patients agreed with our expectations, those for chronic schizophrenics did not, and many controls exhibited a P30 amplitude maximum that was more posterior than anticipated, particularly in the right hemisphere (Fig. 3).

The topography results suggest that the P30 generator is more anteriorly located in nonpsychotic patients than in chronic schizophrenics. Although not statistically reliable, there was also a trend for P30 to peak more anteriorly in latent than in the "other" schizophrenics. The explanation for the posterior distribution of P30 in overt schizophrenics is not readily forthcoming. Although an anatomical difference in the orientation of the probable source in the posterior bank of the postcentral gyrus (Goff et al., 1977) is theoretically possible, one would be more comfortable with a

functional explanation. The topographic differences could result if there were multiple generators for P30 and if the relative balance of activity in these generators differed between groups.

The N60 peak is the last SEP event restricted to the contralateral hemisphere (Fig. 1); it appears to be part of the "primary" complex, like P30. Since N60 was also distributed more posteriorly in chronic schizophrenics than in nonpsychotics or normals (Fig. 3), one may ask to what extent P30 and N60 may reflect the same process. They are probably independent events; their spatial distributions differ (Goff et al., 1977), and we found low correlations between our P30 and N60 measurements. Furthermore although P30 tended to be posteriorly located in the "other" schizophrenic group, that group differed from chronic schizophrenics with respect to N60 (Shagass et al., 1977). This suggests that the diagnostic correlates of P30 and N60 topography are not identical and that there may be some specificity. The findings for psychotic depressives, which revealed no differences from normal in P30 and N60 topography, provide additional evidence favoring diagnostic specificity for the deviant distributions of these peaks.

The results indicating that both P30 and N60 are more posteriorly distributed in chronic schizophrenia may be related to the findings provided by measurements of regional cerebral blood flow (RCBF). Ingvar and Franzen (1974), using intracarotid radioactive isotope injection, and Jacqy et al. (1976), using rheoencephalography, both reported that RCBF was reduced anteriorly and increased posteriorly in chronic schizophrenics. The higher posterior lead amplitudes of P30 and N60 in chronic schizophrenics may thus be paralleled by increased RCBF. This apparent correlation requires experimental confirmation. If one accepts Ingvar's (1975) interpretation of the RCBF differences as indicative of a functional disorder, confirmation of a correlation between RCBF and EP distributions would tend to favor the functional rather than anatomical interpretation of deviant EP topography.

The distributions of SEP peak P90 are of interest in relation to the report by Goff et al. (1977) that this peak (designated by them as P100) appears to consist of a frontal myogenic fraction and a posterior neurogenic fraction. The rather complex distribution patterns found for P90 (Figs. 4 and 5) seem congruent with the idea of two generators and suggest that both the myogenic and neurogenic fractions could have contributed to differences between groups in P90 topography.

The diagnosis by lead interactions found for several later peaks such as SEP N130 (Fig. 4) pose an interpretive problem, as they seem due mainly to low amplitudes at or near the vertex in schizophrenics rather than to clear distribution differences. The statistical topographic effects for these peaks may thus be "artifi-

facts" of amplitude differences. In contrast, the results for VEP peak P300 (Fig. 6) represent a true group difference in spatial distribution. The greatest amplitude of VEP P300 occurred at vertex in controls and at Oz in nonpsychotics and schizophrenics, indicating a more posterior midline distribution in the patients.

Finally, it should be emphasized that this is an initial study and that the specific results require confirmation. However, they indicate that the topographic dimension of EPs merits further investigation.

SUMMARY

This study attempted to determine whether the spatial distributions of somatosensory, visual and auditory EPs differ in relation to psychiatric illness. EPs to intermingled left and right median nerve shocks, checkerboard pattern flashes and binaural clicks were recorded from one EOG lead and fourteen scalp leads in undrugged psychiatric patients and nonpatients. Various age and sex matched clinical groups were compared. To assess topographic differences consecutive peaks in EPs of each type were first detected by visual inspection (cursor program) of certain key leads, and the latencies of the peaks for each subject were then used to measure automatically the amplitudes of events at these times in all leads. To assess group differences in topography, amplitude measurements across leads were subjected to multivariate file analysis. The largest number of topographic differences involved comparisons between chronic schizophrenics, nonpsychotic patients and nonpatients. The distributions of SEP peaks P30, N60, P90, N130 and P180 differed between groups, P30 and N60 being maximal at more posterior locations in the schizophrenics. P300 in the VEP was maximum at the vertex in controls and near Oz in both nonpsychotic and schizophrenic patients.

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CONTRAST EVOKED POTENTIALS AND PSYCHOPHYSICS IN MULTIPLE SCLEROSIS
PATIENTS

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Visual evoked potentials (VEPs) have become widely accepted in recent years in diagnostic schemes for the assessment of multiple sclerosis (MS). It has been shown that for this purpose a deviation in latency is a better criterion than a deviation in amplitude, since amplitude varies widely among subjects, whereas EP latency, especially with contrast stimulation, remains restricted to a rather narrow range. The latency of the EP to stimulation with a reversing checkerboard pattern appears to be increased in 268 out of 393 (= 68%) MS patients (Halliday et al., 1973: 49/51 = 96%; Asselman et al., 1975: 34/51 = 61%; Mastaglia et al., 1976: 34/68 = 50%; Regan et al., 1976: 6/13 = 46%; Lowitsch et al., 1976: 98/135 = 73%; Hennerici et al., 1977: 35/57 = 61%; Duwaer and Spekreijse, 1978: 12/18 = 67%). However, latency increases are not specific for multiple sclerosis since they have also been observed in patients with a variety of other pathologies (Asselman et al., 1975; Halliday et al., 1976). Furthermore, an increased EP latency cannot always be ascribed to an increased conduction time due to demyelination of the optic nerve fibers since a variety of modifications in the stimulus situation - modifications which might also be induced by the presence of pathologies in the subject - may result in an increased EP latency (Duwaer and Spekreijse, 1978). Some examples are given in Fig. 1.

The responses in Fig. 1A show that nonoptimal optical correction can increase the latency of the contrast EP without affecting the shape of the response. This condition mimics what may happen in subjects with lower visual acuity. Furthermore, a reduction of contrast (Fig. 1B) or reduction of the mean luminance level of the checkerboard pattern (Fig. 1C) - conditions which both may simulate

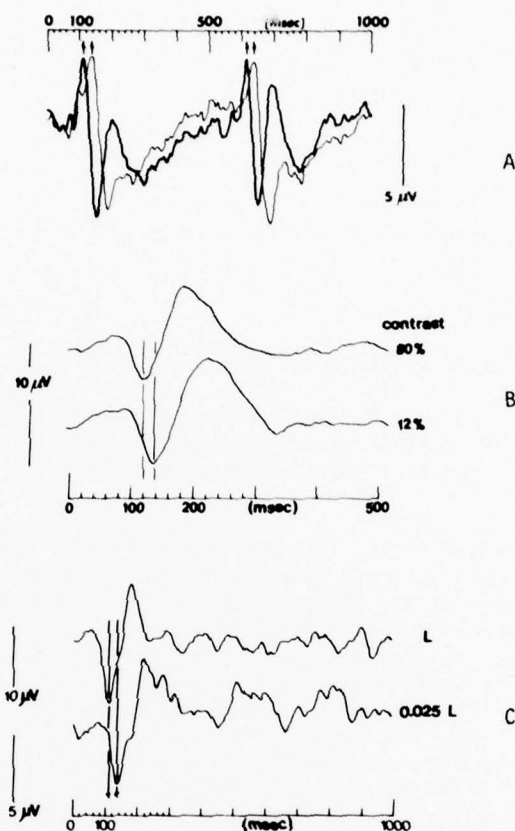
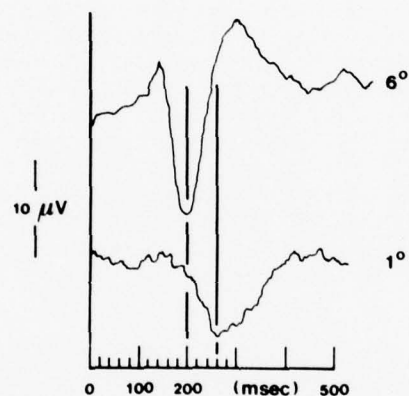
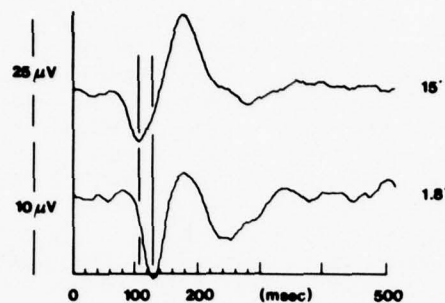


Fig. 1. Examples of peak latency increases and broadening of the contrast EP by manipulation of stimulus parameters. A: Transient (inion-vertex) EPs to pattern reversal (mean luminance 150 asb) in a healthy emmetropic subject with (thin line) and without (heavy line) a cylindrical lens of +3D inserted to blur the horizontal edges of the checks. The binocularly presented checkerboard with 15' checks and 80% contrast reversed with a repetition period of 500 msec. Although the shapes of the responses are rather similar, the latency appears to increase by 25 msec when the lens is inserted. B: Transient (inion-vertex) EPs of a healthy subject to the appearance of a checkerboard (mean luminance 150 asb) with 10' checks at 80% contrast (upper trace) and 12% contrast (lower trace). The checks were presented for 40 msec with a repetition period of 520 msec. The EP obtained at 12% contrast has an 18 msec longer latency than the EP obtained at 80% contrast. C: Transient (inion-vertex) EPs of a healthy subject to the appearance of a checkerboard with



20' checks at 80% contrast and a mean luminance of 200 asb (upper trace) and 5 asb (lower trace), respectively. The checks were presented monocularly once per sec for 40 msec. The low luminance contrast EP has a 25 msec longer latency. D: Transient (inion-vertex) EPs to the appearance of a monocularly presented checkerboard of 80% contrast and checks of 15' (upper trace) and 1.8' (lower trace), respectively. The pattern with a mean luminance of 150 asb was presented for 40 msec with a repetition period of 520 msec. The EP to 15' check presentation has a 20 msec longer latency than the EP obtained with 1.8' checks. E: Transient (inion-vertex) EPs to the appearance of a checkerboard pattern with checks of 15' and 10% contrast. The checkerboard with a mean luminance of 2000 asb was presented for 250 msec with a repetition period of 500 msec. The peak latency of the EP obtained with a stimulus field diameter of 1° has a 40 msec longer peak latency than the 6° field diameter EP. Note the broadening of the response with reduction of stimulus field diameter.

lowered sensitivity - can result in latency increases of the same order as in positive classification of MS patients. The same happens when check size (Fig. 1D) is reduced, a simulation of the situation in amblyopes since mean receptive field diameter varies with eccentricity. Finally, reduction of stimulus field size, simulating visual field defects (Fig. 1E), can cause broadening of the waveform of the contrast EP and a substantial increase of its peak latency. These examples illustrate directly that there can be many causes for the increase of the contrast EP latency and/or broadening of the waveform of the response. Although it cannot be said beforehand whether, in the presence of pathologies in the visual system, broadening of the response or solely a shift in latency will occur, it is our finding that near psychophysical threshold broadening of the response nearly always predominates.

Since contrast EP latency increases can apparently be due to many causes, it might be expected that part of the EP latency increase in MS patients can be attributed to causes other than increased conductance time in optic nerve fibers. Many of these causes can also be detected with other, nonspecific visual tests such as acuity, static perimetry and CFF, as has, in fact, been demonstrated by Lowitsch et al. (1976). It has, therefore, become important to evaluate whether contrast EPs can provide additional information for the diagnosis of multiple sclerosis and to establish whether contrast EP tests can be made more specific for multiple sclerosis by considering features of the response other than latency alone.

In a previous paper (Duwaer and Spekrijse, 1978) we recommended, for MS diagnosis, (a) determination of the apparent latency from the phase spectrum of the responses to checkerboard reversal at repetition rates between 5 and 20 Hz, since in that frequency range the failure rate was found to be minimal, and (b) investigation of the waveform of the transient EP obtained at a low reversal rate. In the present paper we will discuss whether the specificity of the apparent latency data can be improved by also taking into account the shape of the amplitude characteristic obtained with these reversal stimuli. For this purpose, and for an evaluation of additional information provided by EP data, psychophysical data, such as flicker fusion curves (De Lange curves) and perimetric sensitivity profiles, will also be considered.

METHODS

A TV screen (Sony CVM-1810 E, 50 Hz) subtending $8^{\circ} \times 6^{\circ}$ was used to display at a mean luminance of 150 asb a black and white checkerboard pattern of 90% contrast with checks ranging from 15' to 55'. The subjects were asked to fixate upon a pink square of 10', which was positioned approximately in the center of the screen.

The EPs were derived from 2 Ag-AgCl electrodes positioned on the midline at respectively 1 cm and 10-14 cm above the inion, and from a third electrode placed on the right mastoid. An electrode half way between the two midline electrodes served as patient ground. In the text only inion-vertex recordings will be shown. The first mentioned electrode location is the positive one, and the polarity convention adopted in the figures is positive upwards. The bandwidth of the EEG amplifiers was set at 0.5 - 75 Hz; the EP latencies and amplitudes were corrected for the phase shift and amplitude reduction introduced by the low pass fourth order Butterworth filter (Barr and Strout EF 14; cut-off frequency 75 Hz). An HP-2100 computer was used to average the pattern EPs and to determine the phase and amplitude of the first harmonic component in the EPs to check-erboard reversal. Depending on the stimulus condition 40 to 300 EPs were averaged; the reversal rates were fixed by the 25 Hz frame frequency of the TV stimulator at 5.6, 6.2, 7.1, 8.3, 10.0, 12.5, 16.7 and 25 rev/sec. The apparent latency of the EPs to pattern reversal was calculated from the slope of the phase spectrum according to:

$$\text{apparent latency } \tau = \left(\frac{\text{phase difference in degrees}}{\text{frequency interval in Hz}} \right) \times \frac{1000}{360} \text{ msec}$$

The stimulus for the flicker fusion curves was generated by circular fluorescent lamps. The circular sine wave modulated stimulus field of 1° diameter had a mean luminance of 2000 asb and was surrounded by a 25° steady field of 10 times lower luminance level. The visual field plots of the multiple sclerosis patients were determined with the Friedmann analyser (flash duration 300 μ sec) and the Tubinger perimeter (flash duration 500 msec).

RESULTS AND DISCUSSION

Fig. 2 presents some typical amplitude characteristics obtained in three healthy subjects to monocular presentation of the pattern reversal stimulus. Note the substantial interindividual variability in the shape of these characteristics. To compare the amplitude characteristics of healthy subjects and MS patients, the high frequency attenuation was determined for reversal frequencies at 8.3 and 16.7 rev/sec. It was not possible to estimate attenuation over a higher frequency octave since, at the highest reversal frequency of 25 rev/sec that could be produced by our TV stimulator, only rarely could a reliable reversal EP be recorded. Furthermore, the responses at reversal rates of 10 and 12.5 rev/sec had to unfortunately be ignored since these responses can show substantial scatter due to contamination by α -activity. The attenuations determined over the frequency octave from 8.3 to 16.7 rev/sec are presented along the vertical axis in Fig. 3. Along the horizontal axis in this figure the corresponding apparent latencies, estimated over the same frequency trajectory of the phase characteristic, are presented.

In the healthy subjects the mean apparent latency amounts to 109 ± 9 msec. Both the mean and the standard deviation of the apparent latency are somewhat higher than reported in a previous study (105 ± 7 msec; Duwaer and Spekreijse, 1978), since the responses obtained in the frequency trajectory from 5.6 to 8.3 rev/sec were not considered in the present study. With the criterion that apparent latencies can be classified as abnormal when they exceed 3 SD, i.e., reach a value of $\bar{x} + 3\sigma$, the EPs in sixteen out of twenty-three MS patients were classified as deviating. This detection rate of 70% agrees quite well with those reported in literature for non-selected MS patients, classified according to McAlpine's criteria (see introduction). Inspection of Fig. 3 shows, furthermore, that attenuation per se seems to be of no use in clinical diagnosis. Although the scatter is substantial, the data in Fig. 3 show a relation between apparent latency and attenuation. The regression lines in Fig. 3 have a correlation coefficient of 0.4 ($p < 0.1\%$, t-test) and slopes of 0.08 dB/msec and 2.2 msec/dB, respectively. This significant correlation between high frequency attenuation and ap-

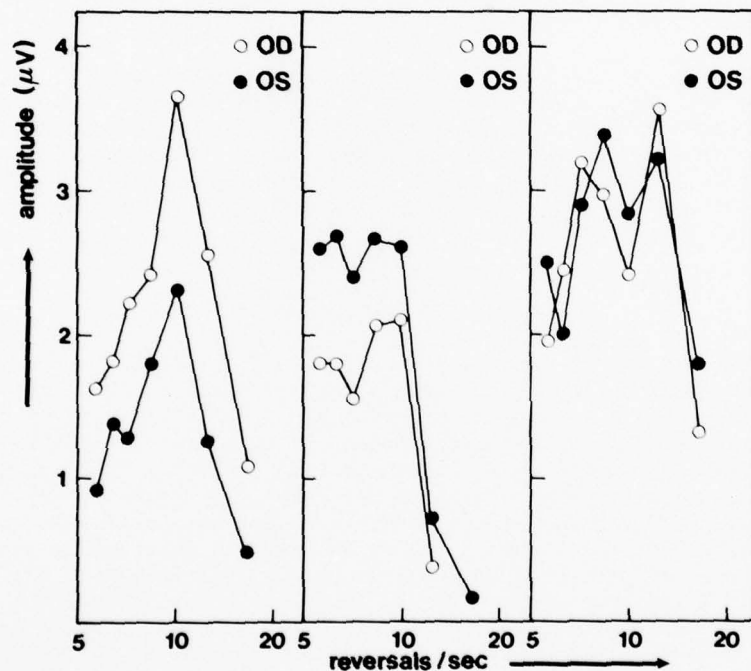


Fig. 2. Amplitude of the first harmonic component in the inion-vertex EP of three healthy subjects as a function of the reversal frequency of a monocularly presented checkerboard with 20' checks of 90% contrast. Note the large interindividual variability.

parent latency suggests that it cannot be excluded that part of the apparent latency increase in MS patients is due to an increase in high frequency attenuation. It should be noted that this can be caused by either a lowering of the cut-off frequency and/or a steepening of the high frequency slope of the amplitude characteristic.

To illustrate how profound the effect of a change in dynamics can be on the apparent latency of the contrast reversal responses, reversal EPs were recorded in four healthy subjects at four levels of mean luminance, ranging from 200 asb to as low as 0.5 asb (intensity range of 2.6 log units). These data, which are presented in Fig. 4, show that a reduction of mean luminance level has a strong effect on both the attenuation and the apparent latency of the reversal EP. Since reduction of luminance results mainly in dynamical changes at distal retinal levels, whereas the pathology in the visual system of MS patients is most likely located in the optic nerve, this result indicates that reduced high frequency sensitivity is not necessarily characteristic for MS.

On the other hand, latency increases can by themselves result in high frequency attenuation. If by progressive demyelination the conduction of times of those optic nerve fibers that serve as input channels for the contrast EP vary substantially, then the steady state EP may be attenuated and the waveform of the transient EP broadened. If for the sake of simplicity the assumption is made that the conduction time across the optic nerve fibers follows a Gaussian distribution, then the frequency components in the contrast EP are attenuated according to:

$\exp \left\{ -\frac{\omega^2 \alpha^2}{2} \right\}$, in which α is the spread in latency in sec, and $\omega = 2\pi f$

with f the frequency in Hz. Since conduction time increases due to demyelination of optic nerve fibers can be at most 30 msec (Ogden and Miller, 1966; McDonald and Sears, 1969, 1970; Rasminsky and Sears, 1972), α is not likely to exceed 10 msec. With $\alpha = 10$ msec the high frequency attenuation over the frequency trajectory from 8.3 to 16.7 Hz is increased by a factor of only 1.5 (3.5 dB). So, conduction time jitter is not likely to explain the frequently observed high frequency attenuation in MS patients. However, increase of conduction time is not the only cause for latency jitter. If, for example, the overall sensitivity is reduced and hence the contrast stimulus closer to psychophysical threshold, then the waveform of the contrast EP generally broadens by much more than 30 msec (see for example Fig. 1E). So, latency jitter cannot, therefore, be excluded as a major cause of increased high frequency attenuation in MS patients.

Due to the large interindividual variability, the shapes of the amplitude characteristics obtained with contrast reversal cannot be used as an interindividual criterion that will be conclusive in

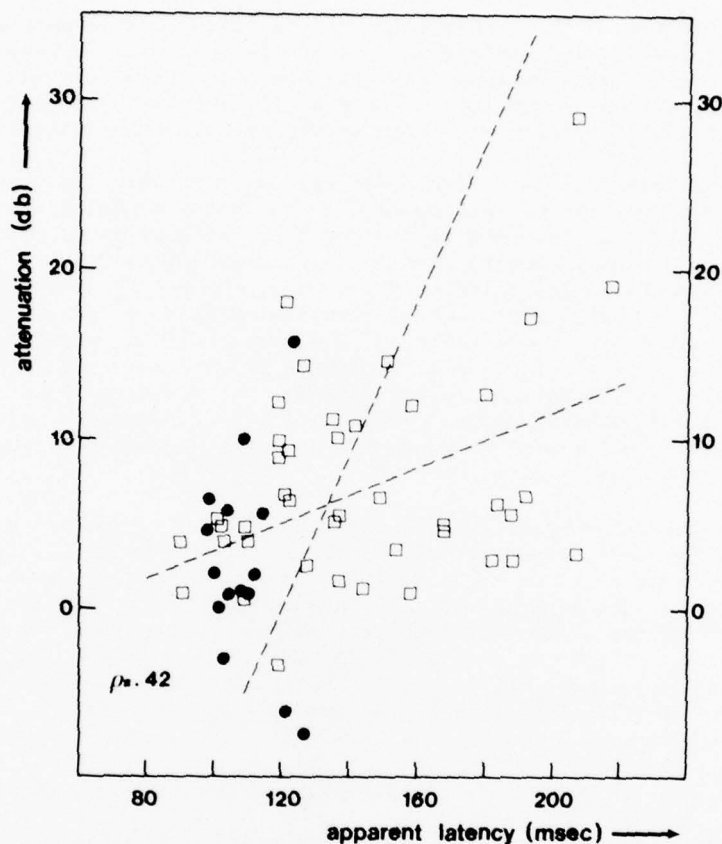


Fig. 3. Amplitude attenuation of inion-vertex EPs to checkerboard reversal is plotted versus the apparent latency of these EPs, which were obtained in eight healthy subjects and twenty-three MS patients. The monocularly presented checkerboard of $8^\circ \times 6^\circ$ consisted of 20' checks at 90% contrast. Amplitude attenuation was calculated from 8.3 to 16.7 rev/sec according to $A = 20 \log A_{16.7}/A_{8.3}$ dB, in which $A_{16.7}$ and $A_{8.3}$ represent the amplitudes of the first harmonic component of the contrast EP to 16.7 and 8.3 rev/sec, respectively. Apparent latencies were calculated from the slope of the phase characteristic of the first harmonic component in the EP to 8.3, 10, 12.5 and 16.7 rev/sec, respectively. The attenuation was plotted in decibels (dB) along the vertical axis and the apparent latency in milliseconds (msec) along the horizontal axis. The data for healthy subjects are indicated by filled circles; those of MS patients by open squares. The regression lines through all data points have the slopes of 0.08 dB/msec and 2.2 msec/dB, respectively. The correlation coefficient amount of 0.42 ($p < 0.1\%$, t -test).

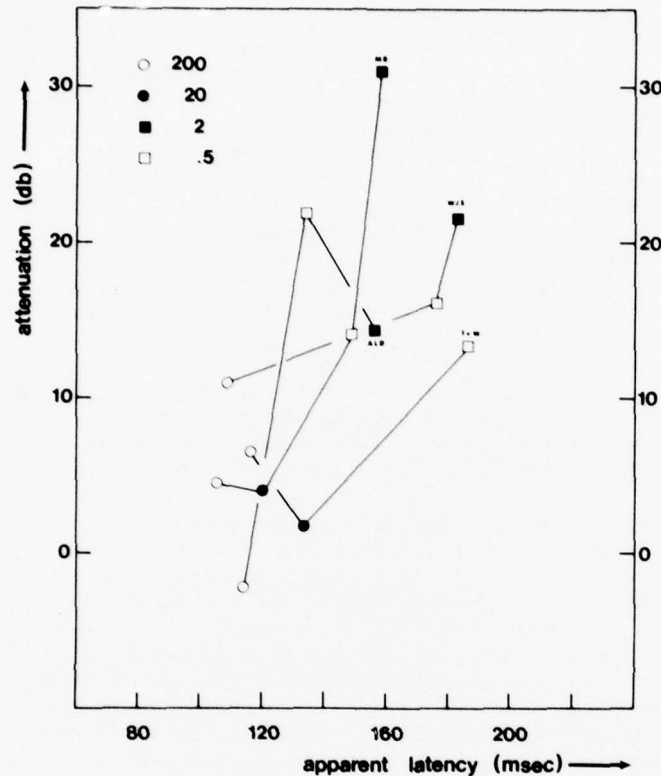


Fig. 4. High frequency amplitude attenuation of inion-vertex EPs to checkerboard reversal is plotted versus the apparent latency of these responses, which were recorded from four healthy subjects. The mean luminance of the monocularly presented checkerboard (20' checks; 90% contrast) was set at four levels of 200 asb (open circles), 20 asb (filled circles), 2 asb (filled squares) and 0.5 asb (open squares), respectively. Throughout the experiments an artificial pupil of 3 mm diameter was used.

attributing latency increases to reduction in high frequency sensitivity. However, inspection of the monocular amplitude characteristics (see Fig. 2) shows that the intraindividual variability is much weaker. So the attribution of latency increases to changes in amplitude characteristics (and vice versa) should be inferred from intraindividual comparison of contrast reversal characteristics. Such an approach may become even more conclusive when psychophysical data such as flicker fusion curves (De Lange curves) and perimetrically determined sensitivity profiles are also taken into consideration.

With regard to the interpretation of the visual field profiles determined with brief flashes (the Friedmann perimeter uses flashes with a duration of 0.3 msec), it should be noted that a reduced sensitivity for these brief flashes can point to both a loss in overall sensitivity (i.e., a reduced gain irrespective of frequency) and to reduced high frequency sensitivity. On the other hand, visual field plots determined with the Tubinger perimeter will be less influenced by sole reduction of high frequency sensitivity, since the Tubinger perimeter employs flashes of 500 msec which contain less high frequencies than brief flashes. So not only can reduced high frequency sensitivity be detected by means of the flicker fusion curves but also by comparison of results obtained with the Friedmann and Tubinger perimeters.

The additional information for the diagnosis of MS that can be gained from considering not only the EP latency but also the contrast EP amplitude characteristic, flicker fusion curve and visual field profile will be exemplified by results obtained in three MS patients.

The first case is a definite MS patient according to McAlpine's criteria. Stimulation of the left eye of this patient gives a deviating flicker fusion curve (Fig. 5A). Not only is the overall sensitivity reduced by about a factor of 5, but there is also a substantial loss of high frequency sensitivity. Furthermore, the peak latency of the transient reversal EP upon stimulation of the left eye is increased (interocular latency difference of 44 msec; Fig. 5B), and also the apparent latency is abnormal (interocular latency difference of 71 msec, Fig. 5C). Finally, the amplitude characteristic upon reversal stimulation of the left eye shows pronounced loss of high frequency sensitivity (interocular attenuation difference from 8.3 to 16.7 rev/sec amounts to 19 dB; Fig. 5D). From these data it is evident that the latency increase of the left eye contrast EP is at least partly due to increased high frequency attenuation. Further inspection of the flicker fusion curves reveals an interocular attenuation difference of about 3 dB in the frequency range from 4 to 8 Hz and of about 15 dB over the trajectory from 8 to 16 Hz. The latter attenuation difference is more compatible with the interocular attenuation difference of the EP amplitude characteristic than the former one. This suggests that the pathology in the visual system of this patient operates upon the reversal frequency instead of the luminance modulation frequency of the individual checks in the reversing checkerboard. Since this patient had suffered from left eye optic neuritis, the origin of the increased high frequency attenuation is most likely the optic nerve. This implies that an analysis of signal processing in the optic nerve to a reversal stimulus should be based upon the dynamics at contrast frequencies.

The second case is a definite MS patient whose right eye has an abnormal sensitivity profile with scotoma in separate segments of

the visual field (Fig. 6A). Also the peak latencies of the right eye transient reversal EPs are abnormal (for checks of 55' the interocular latency difference amounts to 40 msec; Fig. 6D). However, the apparent latencies derived from high reversal rate EPs are normal (right eye 119 msec; left eye 121 msec; Fig. 6C), and the corresponding amplitude characteristics have the same slope (Fig. 6B). So, on the sole basis of apparent latency of the reversal EPs this patient would have been classified as normal. However, inspection of the amplitude characteristics shows that at progressively lower reversal rates the interocular amplitude difference gradually disappears. This suggests that the optic nerve fibers that transmit the signals which finally result in the contrast EP can be roughly divided into two populations: one with normal conduction time and high frequency sensitivity and the other with increased conduction time and reduced high frequency sensitivity. At low reversal rates both populations contribute to the response, resulting in a broadening of the transient contrast EP and roughly similar EP amplitudes. At high reversal rates only the normal population initiates the contrast EP resulting in normal apparent latency and normal high frequency attenuation, although, of course, the amplitude of the response is smaller. This hypothesis is supported by the sensitivity profile of the right eye of this patient which, indeed, shows patchy scotomata in the central 8° of the visual field, i.e., the retinal region from which contrast EPs can be recorded.

The third case is a probable MS patient whose flicker fusion curves (Fig. 7A) and EP amplitude characteristics (Fig. 7B) seem rather similar for stimulation of either eye. Yet the apparent latencies (left eye 207 msec; right eye 188 msec; Fig. 7C) and the peak latencies of the transient reversal EPs (left eye 177 msec; right eye 158 msec; Fig. 7D) are quite abnormal. So, this patient seems to be one of the rare cases in which latency increase is not accompanied by a loss in high frequency sensitivity.

The above results show that part of the latency increases of the contrast EPs in multiple sclerosis patients are accompanied by reduced sensitivity and increased high frequency attenuation. A latency increase of contrast EPs seems, therefore, to imply deviating results in standard methods of testing visual functioning, in particular static perimetry. This has been confirmed in twelve MS patients by direct comparison of EP latency and sensitivity profiles obtained with static perimetry. In all patients with increased EP latency (eight out of twelve), sensitivity appears to be reduced in the central 10° of their visual field. In nine out of eleven eyes with increased contrast EP latency, sensitivity was also reduced outside the central 10° region. In one patient with normal EP latency, sensitivity was reduced in the central 10° . Comparison of the results obtained with the Friedmann perimeter (pulse width 300 msec) and those obtained with the Tubinger perimeter (pulse width 0.5 sec) shows that in these patients abnormalities are always de-

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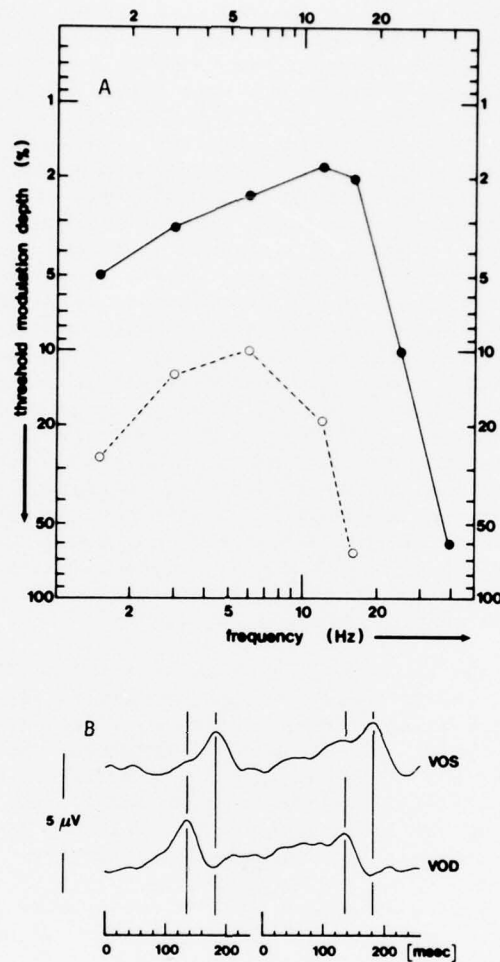
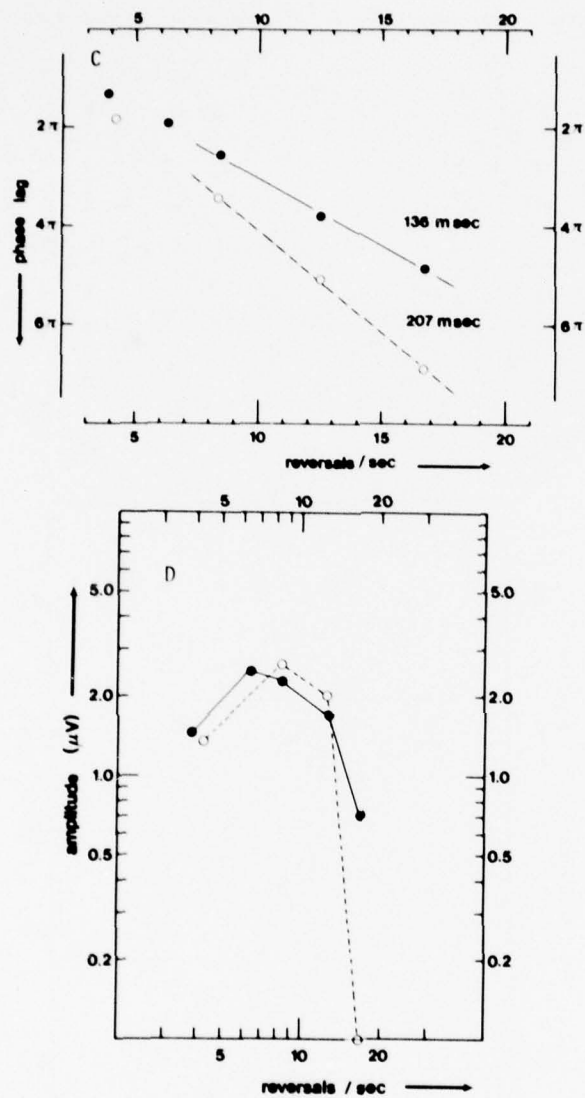


Fig. 5. Psychophysics and electrophysiology of a definite MS patient. A: Threshold modulation depth is plotted as a function of the frequency of a sinusoidally modulated, homogeneously illuminated test field with a diameter of 1° and a mean luminance of 2500 asb. The left eye flicker fusion curve (open circles, dashed line) has a lower sensitivity and cut-off frequency than the "normal" right eye curve (filled circles, solid line). B: Inion-vertex EPs to monocular stimulation with 20' checks at 90% contrast reversing at a rate of 3.85 rev/sec. The peak latency of the first positive component in the left eye EP (upper trace) amounts to 180 msec and that of the right eye EP is 136 msec (lower trace). C: Phase lag of the first harmonic component in the inion-vertex EP as a function of the re-



versal frequency of a monocularly presented checkerboard with 20' checks at 90% contrast. The slope of the right eye phase characteristic (solid line) gives an apparent latency of 136 msec, that of the left eye (dashed line) of 217 msec. D: Amplitude of the first harmonic component of theinion-vertex EPs is plotted versus the reversal frequency of a monocularly presented checkerboard with 20' and 90% contrast. The amplitude attenuation between 3.3 and 16.7 rev/sec amount to 29 dB for the left eye (dashed line) and 10 dB for the right eye (solid line).

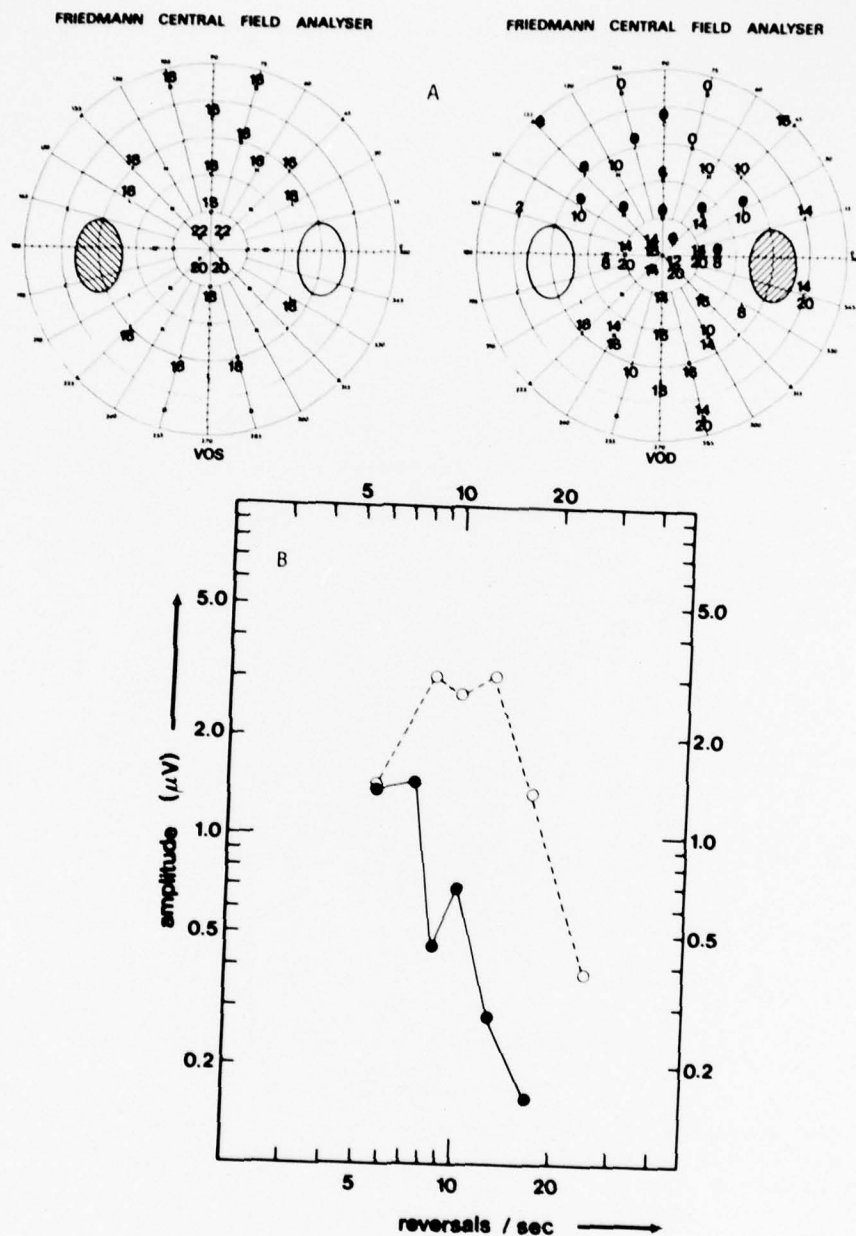
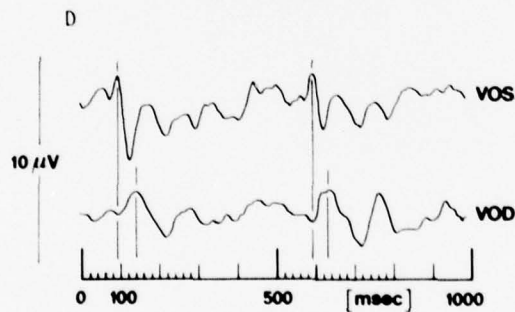
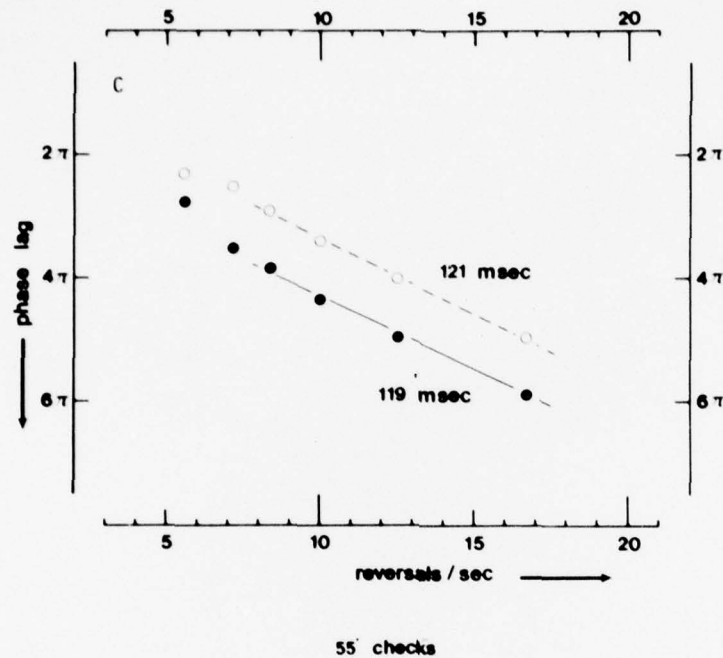


Fig. 6. Psychophysics and electrophysiology of a definite MS patient. A: The visual field plots were determined with the Friedmann analyzer. The numbers are a measure for sensitivity in log units (e.g., 2.0, 1.8, 0.8). B: Amplitude characteristics of inion-vertex EPs to monocular checkerboard reversal (stimulus conditions



as in Fig. 5D). The amplitude attenuation between 8.3 and 16.7 rev/sec amounts to 6.3 dB and 8.9 dB for left eye and right eye, respectively. C: Phase characteristics of inion-vertex EPs to monocular checkerboard reversal (stimulus conditions as in Fig. 5C). Apparent latencies amount of 119 msec and 121 msec for right and left eye, respectively. D: Inion-vertex EPs to monocular stimulation with 55' checks at 90% contrast, reversing at a rate of 2 rev/sec. The peak latency of the first positive component in the left eye EP amounts to 90 msec; that of the right eye EP is 135 msec.

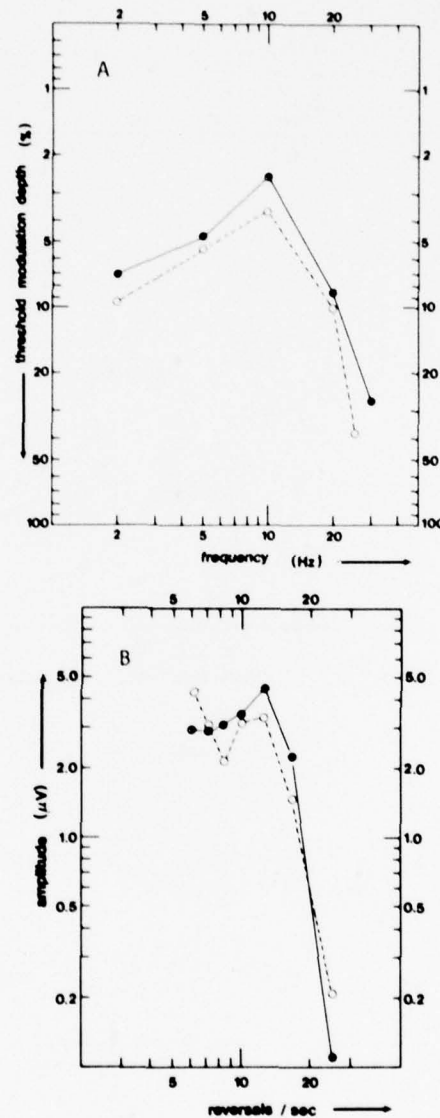
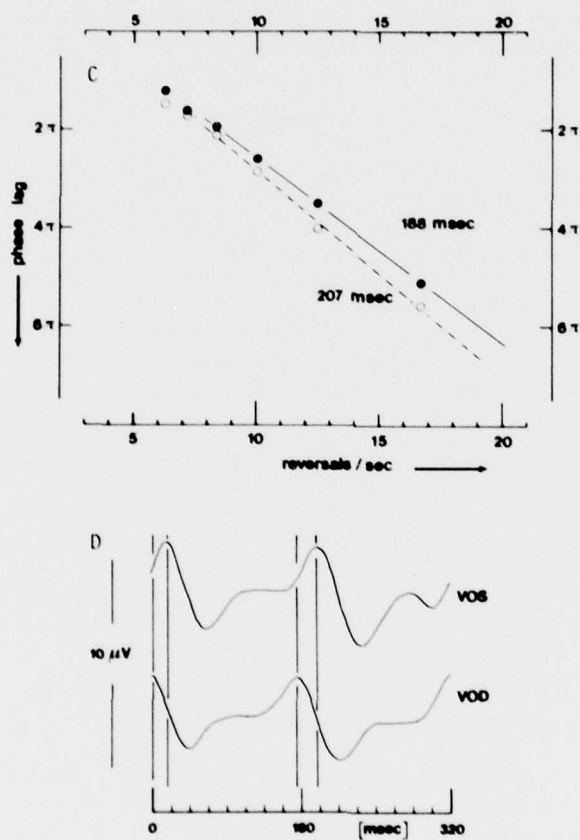


Fig. 7. Psychophysics and electrophysiology of a probable MS patient. A: Flicker fusion curves to separate stimulation of right (filled circles and solid line) and left eye (open circles and dashed line). For stimulus conditions, see Fig. 5A. B: Amplitude characteristics of inion-vertex EPs to monocular checkerboard reversal. For stimulus conditions, see Fig. 5D. The amplitude attenuation between 8.3 and 16.7 rev/sec amounts to 3.3 dB and 2.9 dB for left and right eye, respectively. C: Phase characteristics



of inion-vertex EPs to monocular checkerboard reversal. For stimulus conditions, see Fig. 5C. Apparent latencies amount to 188 msec and 207 msec for right and left eye EPs, respectively. D: Inion-vertex EPs to monocular stimulation with 20' checks at 90% contrast, reversing at a rate of 6.25 rev/sec. The peak latency of the first positive component in the left eye EP (upper trace) amounts to 177 msec and that of the right eye EP (lower trace) is 159 msec.

tected with both perimeters. This suggests that for the multiple sclerosis patients studied, increased high frequency attenuation only rarely occurs without a reduced overall sensitivity. Similar results have been described by Lowitsch et al. (1976). In their study, sixty-four out of seventy-one MS patients with abnormalities in Goldmann perimetry showed increased contrast EP latency. Their publication does not provide the combined detection rate of Friedmann and Goldmann perimetry. Their data do show, however, that the detection rate on the basis of contrast EP latency (98 out of 135) is only slightly higher than the combined detection rate of other, nonspecific methods of testing visual functioning (95 out of 135).

SUMMARY

Our data indicate that additional information can be gained for the diagnosis of MS by considering not only the apparent latency of the contrast reversal EPs, but also their amplitude characteristics. Results obtained from twenty-three MS patients indicate that the latency increase of the contrast EP may be accompanied by increased high frequency attenuation or by a reduced overall sensitivity. The latter has been confirmed in another group of twelve MS patients of whom all eight with increased contrast EP latency had a lower sensitivity in static perimetry.

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EVENT RELATED POTENTIALS IN DEVELOPMENT, AGING AND DEMENTIA

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An abnormal response to sensory information can result from deficits in sensory transmission, cognitive processing or response production. Recently it has become feasible to comprehensively evaluate sensory transmission using event related potentials (ERPs). With ERP techniques the functioning of the afferent pathways can now be reliably determined, and lesions in the pathways can, in many instances, be precisely localized (see Starr, 1978 for review). Among neurological patients, however, the problem often lies at one of the two remaining stages about which ERP procedures currently in clinical use provide little information. Among these patients, differentiating those with real deficits in cognitive function from those who are unable to interact with the examiner due to motor or language deficits, or who are unwilling to cooperate, is often a difficult and subjective task. Direct recording of brain activity in the form of ERPs is one way to overcome such obstacles of communication and cooperation since it requires no overt response on the part of the patient and only a modicum of cooperation. Also, since certain "endogenous" components of the ERP have been unequivocally associated with cognitive activity in a wide variety of studies (see Donchin et al., in press, and Tueting, in press, for reviews), it is now possible to unobtrusively monitor cognitive activity as well as sensory function. The purpose of the studies described here was to determine the feasibility of utilizing the endogenous components of the ERP as an objective measure of mental function in neurological diseases which produce cognitive deficits.

AGE AND ERPS

In the early stages of this work it became evident that age

has significant effects on the endogenous components. Similar observations have recently been made by others, both with respect to aging in adults (Brent et al., 1976; Ford et al., in press; Marsh and Thompson, 1972; Pfefferbaum et al., in press) and with respect to development in children (Courchesne, 1977; Karrer and Ivins, 1976; Shelburne, 1973), though age effects have not been systematically studied across the complete lifespan.

In order to evaluate the effects of age on both the exogenous and endogenous components of the ERP, forty-seven normal subjects between the ages of 6 and 76 years were tested (Goodin et al., 1978). Trains of tonal stimuli (60 dB SL) were presented through earphones. Eighty-five percent of the tones had a frequency of 1000 Hz, and 15% had a frequency of 2000 Hz; the subjects were asked to count the occurrences of the rare tones. ERPs were averaged separately for the rare and frequent tones in each condition.

The ERPs of one subject are shown in Fig. 1. All waveforms were characterized by the exogenous N1 and P2 components of the auditory "vertex" potential. The rare tone was also associated with a prominent endogenous P3 component, reflecting the differential cognitive processing of that tone. In Fig. 2 the rare tone

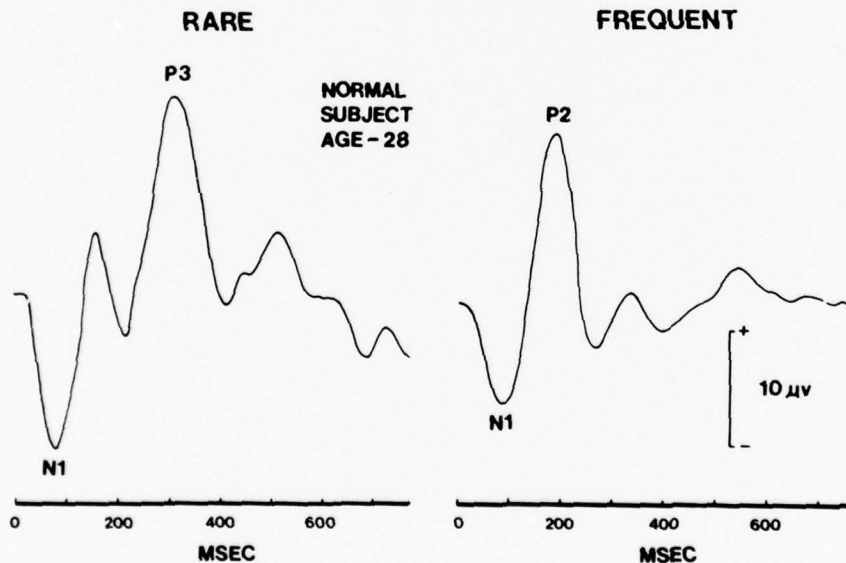


Fig. 1. ERP waveforms for one subject (Cz-linked mastoids) for the rare and frequent tones.

waveforms are shown for six adult subjects. These data illustrate one of the primary results of the study. For adults there was a systematic shift of the P3 component to longer latencies ($p < .001$) with increasing age (top to bottom). The P3 latency for young

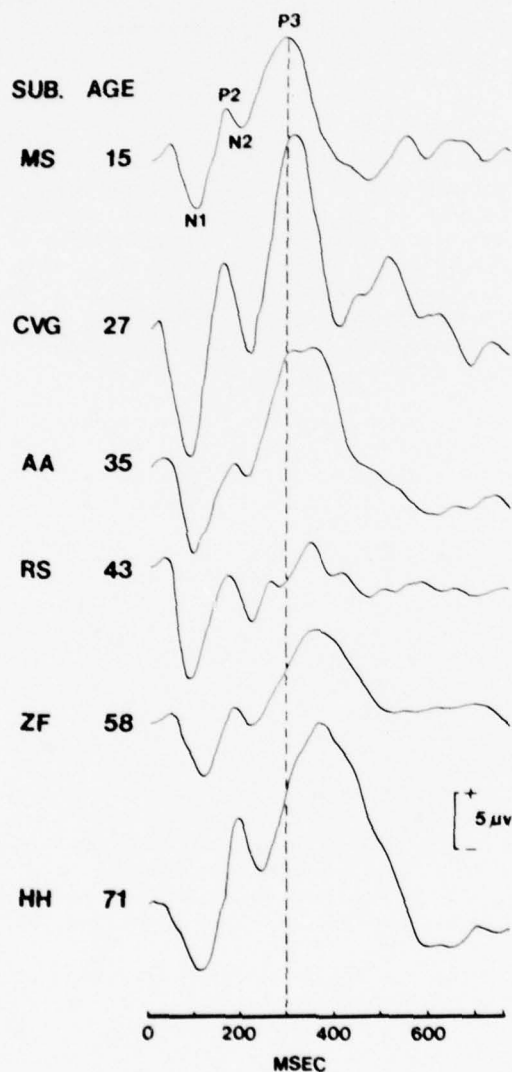


Fig. 2. Rare tone ERPs for six subjects shown in the order of increasing age (top to bottom).

adults (15 to 20 years) was approximately 300 msec, but it increased to 400 msec or more by the seventh decade. The effects of age on the latencies of all components are shown in Fig. 3. Significant increases in latency with increasing age were also found for the N2 ($p < .001$) and P2 ($p < .001$) components of the ERP, though the magnitude of the age related latency increase diminished for successively earlier components. The N1 component, in fact, showed only a nonsignificant trend toward longer latencies with increasing age.

Quite a different picture of the effects of age on the latencies of ERP components emerged for the subjects between the ages of 6 and 15 years (also shown in Fig. 3). The latency of the P3 component decreased markedly with age ($p < .001$), as did the latency of the N2 component ($p < .05$). The combined result of the developmental and aging effects on these components was that the minimum N2 and P3 latencies were recorded from subjects in their mid- to late teens. Developmental changes in the N1 and P2 latencies were not significant, though such effects cannot be ruled out because of the small number of young subjects in the study.

The increases in the N2 and P3 latencies with increasing age in adults were paralleled by a significant ($p < .01$) decrease in the peak-to-peak N2-P3 amplitude. There was also a significant decrease ($p < .05$) in the N1-P2 amplitude with age in adults.

In summary, age change was found to have significant effects on the latencies and amplitudes of the various ERP components. The most dramatic changes were in the latencies of the endogenous N2 and P3 components. During childhood the latencies of the N2 and P3 components decreased markedly (at a rate of 12.3 and 18.4 msec/year, respectively). This result is consistent with those reported by Courchesne (1977) and Shelburne (1973). The latency decreases for N2 and P3 during childhood were followed by gradual increases in N2 and P3 latencies with increasing age (at a rate of 0.79 and 1.64 msec/year, respectively). This effect of aging is also consistent with the results of other studies (Brent et al., 1976; Ford et al., in press, this volume; Marsh and Thompson, 1972). The particular value of this study, however, is that a common procedure was used to test subjects of all ages so that the biphasic nature of the age related latency changes were clearly evident.

Numerous alterations in the central nervous system at the tissue level and subcellular level occur over the lifespan which might account for these changes in the latency of neural events (see Terry and Gershon, 1976, and Ord and Brizzee, 1975, for reviews). Unfortunately a correlation between effects on scalp recorded events and changes at the cellular level or even in the cortical mantle is a step which cannot be made. It is, however,

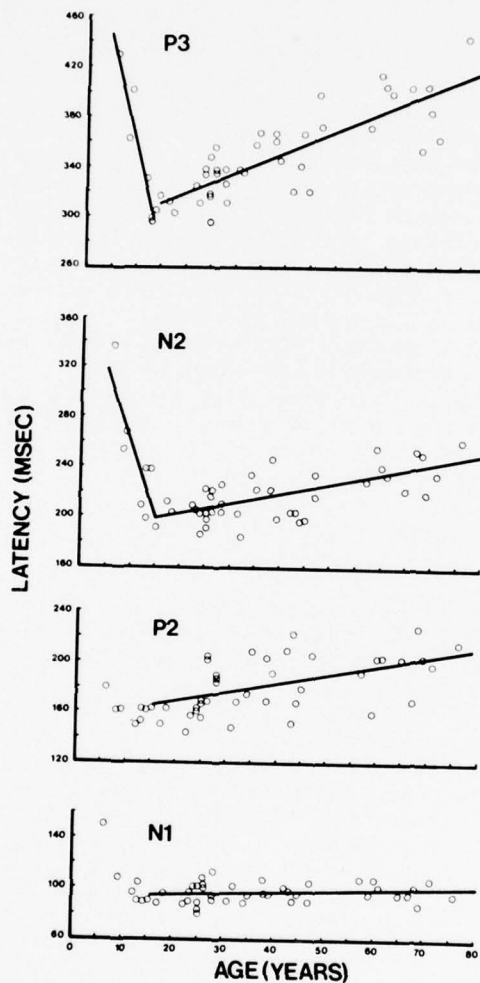


Fig. 3. Latencies of ERP components as a function of age. Regression lines were calculated separately for subjects less than and greater than 15 years of age. The N2 and P3 latencies were derived from the rare tone ERP waveform. The N1 and P2 latencies were measured from the frequent tone ERP waveform.

possible to relate the age related latency changes in the endogenous potentials to functional changes in the relative timing of cognitive processes.

Correlations between P3 latency and decision latencies, as assessed by behavioral reaction time measures, have been reported on several occasions (Kutas et al., 1977; Ritter et al., 1972; Roth et al., 1978; N. Squires et al., 1977). The extension of that relationship to the data of this study would suggest that a decrease in the speed of cognitive processes occurs with advancing age in adults. This suggestion has been made on the basis of reaction time data alone (see Botwinik, 1973, for a review), and Ford et al. (in press) have discussed the issue in relation to age related changes in both the P3 and reaction time latencies in a memory retrieval task. Choice reaction times for children are also reported to decrease with age in a manner similar to the latency decreases of the N2 and P3 potentials reported here (Bohle, 1967). Moreover, in cases where P3 and reaction time latencies are not perfectly correlated it appears that the P3 latency is more specifically related to the timing of cognitive activity than is the reaction time since the latter measure is additionally affected by many variables, only some of which are cognitive in nature (e.g., response selection) while others are related to physical variables affecting the motor pathways (Ford et al., in press).

The slowing of cognitive processing in normal aging is presumed to be independent of decreased auditory sensitivity with age (Corso, 1971). All of the subjects in this study reported that they could hear the tones clearly and had no difficulty discriminating their pitches. In order to evaluate the effects of stimulus intensity, however, three subjects were tested in a series of conditions in which the stimulus intensities were lowered in 10 dB steps. The result was that the P3 latency remained constant until the tone intensities were within 15 dB of threshold, at which time the P3 latency increased by an average of 15 msec. With the decrease in signal intensity, however, there was an increase in the N1 latency of nearly 40 msec. No comparable latency change for N1 was found as a function of increasing age (Fig. 3).

MENTAL FUNCTION AND ERP'S

Two groups of patients were tested in order to determine whether the P3 latency might be useful as an objective measure of mental function in neurological disease (Goodin et al., in press). The first group of patients consisted of thirty-two individuals ranging in age from 25 to 84 years who were diagnosed as having decreased mental functioning (dementia). Their mental function was further quantified with the Mini-Mental Exam (Folstein et al., 1975). The

diagnoses and mental status examination scores for these patients are shown in Table I. The mean score for the demented patients was 20.7 out of the possible 30 points on the examination. For comparison normal subjects usually scored either 29 or 30 points on the test.

The second group of patients consisted of thirty-one individuals ranging in age from 19 to 78 years with no discernible deficits in mental function. The diagnoses and mental status scores for this group are shown in Table II.

The testing procedure was the same as used for the normal subjects. While the task was not difficult for most subjects, some demented patients had to be frequently reminded of the task, and their counts were not accurate. These reminders seemed adequate since the patients were cooperative and eager to please. From an

Table I. Diagnoses and mental status examination scores of the demented patients.

	Number	MMS	AP3(e)
Senile and Pre-Senile Dementia	10	19.4**	+2.58***
Metabolic Encephalopathy*	6	21.5	+3.71***
Hydrocephalus	6	21.1	+2.93
Cerebro-Vascular Disease	2	21.5	+3.06
Brain Tumor	1	17.0	+4.00
Herpes Simplex Encephalitis	1	20.0	-0.29
Uncertain Etiology	6	21.8**	+4.64
Mean	32	20.7	+3.23

* Hypothyroidism, alcoholic with severe electrolyte disturbances, anoxia, steroid encephalopathy.

** One patient could not be tested and is not included in the calculations.

*** One patient could not be assigned a P3 latency and is not included in the calculations.

Table 2. Diagnoses and mental-status examination scores of the non-demented patients.

	Number	MMS	$\Delta P3(\sigma)$
Multiple Sclerosis	5	29.0	+0.39
Depression	5	28.6	-0.36
Cerebrovascular Disease	3	28.7	-0.26
Parkinson's Disease	4	29.5	+0.76
Schizophrenia	3	27.5**	+0.50
Hydrocephalus	1	29.0	-0.93
Porencephalic Cyst	1	30.0	+0.83
Miscellaneous*	9	29.4	+0.03***
Mean	31	28.8	+0.14

* Diabetic neuropathy, casalgia, bilateral subdural hematoma, diffuse cortical atrophy, anosmia with left arm weakness, gait apraxia, vertigo, Huntington's Chorea.

** One patient could not be tested and is not included in the calculations.

*** One patient could not be assigned a P3 latency and is not included in the calculations.

operational point of view the task appeared to have the desired effect. Namely, it induced the patients to attend to the auditory stimuli and elicited differential processing of the rare and frequent tones (as indicated by the presence of P3 components).

The P3 latencies of all of the patients are shown in Fig. 4. The data for the normal subjects (greater than age 15) tested previously are represented by regression lines and lines indicating one and two standard deviations from normal which are superimposed on the data for the demented patients (top) and non-demented patients (bottom panel).

It should be noted that of the fifty-nine patients tested, a reliable measure of the P3 latency was impossible for only three patients: two demented patients and one non-demented patient. One of the demented patients would not remain still during the test. Consequently the waveforms were contaminated by muscle artifact. For the other two patients, the ERP waveform consisted of the N1

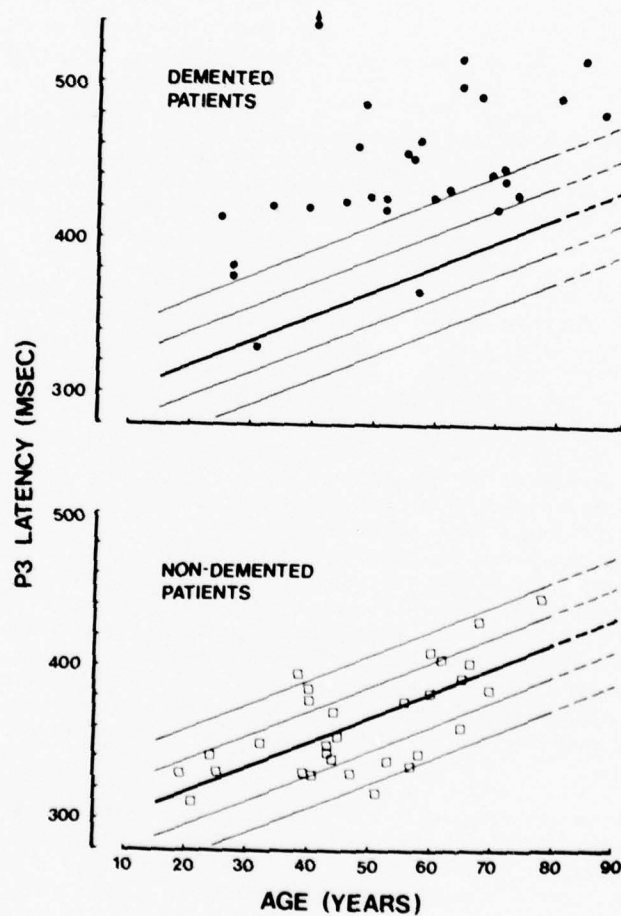


Fig. 4. Latency of the P3 component as a function of age for demented patients (top) and non-demented patients (bottom).

and P2 potentials followed by a broad positivity between 300 and 500 msec without any clear peak.

The distribution of P3 latencies for the non-demented patients and the normal subjects were essentially identical. For the demented patients, however, the P3 latencies were uniformly long relative to normal. The average P3 latency for the demented patients exceeded the latency derived from the normal regression line by 3.23 standard deviation units. Of the thirty demented patients with definable P3 components, twenty-five (or 83%) had P3 latencies that exceeded the norm by 2 or more standard deviations. This occurred only once among the non-demented patients, which would be expected on statistical grounds. The mean P3 latency deviations from normal for the various subgroups of patients are presented in Tables I and II.

The amplitude of the P3 component for the demented patients was also found to be significantly ($p < .05$) smaller than normal. The mean difference, however, relative to the normal variability of the P3 amplitude, was small compared to that for the P3 latency.

The patients tested in this study were pre-screened only to the extent of eliminating those who were sufficiently uncooperative to submit to testing or had gross involuntary movements which might have interfered with the recordings. Thus the composition of patients in the various diagnostic groups, and the results for each, can be considered representative of the population that might be encountered. In that respect, there is a remarkable consistency among the results for the demented patients, regardless of etiology. Apparently a slowing of cognitive function is a consistent effect of most of the dementing processes studied here. On the other hand, in cases where there were apparent, but not actual, deteriorations in mental function due to psychiatric disorders (such as depression or schizophrenia or motor disorders such as Parkinson's disease), there was no change in the latency of the P3 component (see Table II). On the basis of this sample of patients, a reasonable criterion for electrophysiologically defining dementia might be a P3 latency 2 standard deviations greater than normal. With such a criterion, approximately 80% of the demented patients would be correctly classified with an expected false alarm rate of about 5%.

We have also followed a few patients over sufficient periods of time to observe correlations between changes in mental function and P3 latency. One patient, for instance, has shown a marked improvement in mental status over the period of a year following a successful surgical procedure for hydrocephalus, with a corresponding shift in the P3 latency from late to within the normal range. There have likewise been instances of a decline in mental function associated with an increase in P3 latency, or even the disappear-

ance of the component.

There remain a number of questions regarding the five patients in this study who were clinically demented but who fell within the normal range according to the measure of P3 latency. No consistent pattern of etiology or test scores was found that could categorize these patients. This lack of correspondence between the test score and the electrophysiological measure probably reflects a weakness in the brief procedure for testing mental status which might be eliminated by a more comprehensive mental status test. Clearly all aspects of mental function cannot be covered by a thirty-point test. This was quite evident in the case of the nearly pure amnesic syndrome found in the one patient who had experienced an episode of herpes simplex encephalitis. This patient (age 31) had a normal latency P3 component, as shown in Fig. 4 and Table I. Quite significantly, this patient also had no difficulties with the processing of information as long as a memory component was not involved. In such a case a speed measure of cognitive activity such as P3 latency apparently does not reveal the patient's deficit in mental function.

It should be recognized that the distinctions made here, at least for individual patients, were not possible based upon analysis of the exogenous components of the ERP. There were no differences in the N1 or P2 amplitudes or latencies among the groups. In many cases of dementia the sensory pathways are relatively unaffected. In any case, it seems most reasonable to test mental function with a procedure that challenges the patient's mental capabilities and, as a result, elicits endogenous potentials.

The results of these two studies suggest a variety of applications of the endogenous ERP components to the assessment of mental function. During childhood there is a sufficiently rapid decrease in P3 latency that relatively fine distinctions regarding the course of an individual child's development might be possible. Such a measure could supplement the standard psychometric tests of development and may be particularly useful in difficult patients with language or motor deficits. Some applications of similar procedures to mental retardation are discussed elsewhere in this volume (N. Squires et al.).

The procedures described here are only a first attempt to use endogenous potentials to evaluate mental function in a clinical situation. It can reasonably be expected that more nearly optimum conditions might be found that would decrease the reliability and sensitivity of the procedure. In addition, higher levels of mental function may be accessible for testing if linguistic stimuli, rather than simple tones, are used since normal subjects are able to categorize rare and frequent stimuli on the basis of their linguistic

attributes, thus producing P3 results similar to those shown here (Kutas et al., 1977). It is thus foreseeable that a battery of tests might be developed around a common basis of rare and frequent events to evaluate successively higher cognitive functions.

SUMMARY

The feasibility of using event related potentials to provide an objective means for assessing normal and abnormal changes in cognitive function associated with development and aging is examined. Of the numerous waveform amplitude and latency measures obtained, the latency of the P3 component (latency 300-500 msec) was found to be the most sensitive to variations in age. The shortest P3 latencies were found for subjects in their late teens with a sharp decrease in latency between ages 6 and 15 followed by a more gradual increase in latency with increasing age beyond age 15. For demented patients the P3 latency substantially exceeded the normal value for their age in more than 80% of the cases. The P3 latency recorded from the patients without dementia, however, did not differ significantly from the normal values. The latencies of the earlier, stimulus related components did not differentiate either patient group from normal.

ACKNOWLEDGEMENTS

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EVENT RELATED POTENTIAL ASSESSMENT OF SENSORY AND COGNITIVE
DEFICITS IN THE MENTALLY RETARDED

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The application of event related potential (ERP) techniques to the mentally retarded presents a somewhat different challenge to the electrophysiologist than does the application of ERPs to other clinical populations. In particular, while differential diagnosis is of major interest in the investigation of such problems as minimal brain damage (MBD), schizophrenia and dementia, diagnosis is of less importance in mental retardation. What is important is to differentiate among the different types of information processing deficits occurring in the retarded so that educational remediation may be designed on an individual basis to compensate for sensory and intellectual inadequacies.

Recent advances in our understanding of the determinants of the human ERP suggest that electrophysiological techniques may be useful in untangling the web of cognitive and perceptual problems exhibited in the retarded population. The ERP consists of a series of components that reflect the successive activation of different neural generators. Some of these components, such as the auditory far field response, are primarily sensitive to variations in stimulus parameters and have thus been labeled "exogenous" components. These components have proven to be well suited for the assessment of basic sensory function (e.g., Picton et al., 1977) and in the identification of localized brain lesions (Sohmer et al., 1974; Starr and Hamilton, 1976; Sohmer and Student, 1978). Other components, termed "endogenous", have been shown to depend primarily on the meaning the stimuli have for an individual (Tueting, in press; Donchin et al., in press). Experimental studies in normal adults suggest that the endogenous components may be useful in the assessment of attention, memory and perception.

The major advantage ERP techniques have over more traditional methods of assessing mental functions in the retarded is twofold. First, since retarded individuals are likely to suffer from multiple deficiencies, including problems of motor control, it is difficult to identify a behavioral deficit with a particular processing stage. Most ERP components are independent of motor output variables and, within certain broad limits, are also independent of each other, making it possible to tap into single information processing stages. Second, since problems with speech reception and production are almost universal in the retarded, traditional testing techniques which rely heavily on verbal instruction and verbal report are unsuitable while ERP measurement requires only a minimum of verbal interaction.

In our laboratory we are investigating a variety of ERP components in the severely and profoundly retarded in order to develop a battery of ERP assessment techniques that may be useful in evaluating a broad range of sensory and cognitive functions in the retarded. Two of those experiments will be reported here.

EXPERIMENT I: BRAIN STEM AND CORTICAL ERPS TO MONAURAL AND BINAURAL AUDITORY STIMULATION

The first seven vertex positive waves of the human auditory evoked response occur within 10 msec following a brief auditory stimulus (Sohmer and Feinmesser, 1967; Jewett et al., 1970; Jewett and Williston, 1971). The evidence increasingly supports the conclusion that these waves reflect the activation of successive brain stem auditory nuclei (Jewett, 1970; Lev and Sohmer, 1972; Buchwald and Huang, 1975). Since brain stem structures have been implicated in retardation on both neuroanatomical and neurological grounds, abnormalities in these potentials in retarded individuals might be useful in localizing their problems to particular brain locations. The current experiment sought to make this comparison under conditions in which the potentials would be likely to reflect a fundamental aspect of auditory information processing, the integration of binaural information.

Interactions in the acoustic input from the two ears have been demonstrated at widespread levels of the brain stem auditory pathway, including the superior olive (e.g., Galambos et al., 1959) and the inferior colliculus (e.g., Erulkar, 1959). At each level these interactions may be either excitatory or inhibitory. Recent evidence suggests that binaural auditory experience early in life is essential for the development of normal binaural processing in the rat (Silverman and Clopton, 1977; Clopton and Silverman, 1977). On the basis of the latter data, the retarded might be expected to have a higher incidence of acquired as well as congenital defects of binaural processing.

Two experiments in the cat (Jewett, 1970; Huang and Buchwald, 1978) have reported indications of binaural interactions in the surface recorded potentials. In both cases the amplitude of wave IV was reduced during simultaneous stimulation of both ears compared to the algebraic summation of the potentials to left and right ears when stimulated separately.

Method

Seventeen institutionalized Down's syndrome individuals were brought to the laboratory for evoked response assessment. Four proved uncooperative, and two were subsequently deleted from the study due to probable left/right hearing asymmetries (defined as a wave V latency difference greater than .5 msec between the two ears). This left eleven subjects with usable data. The mean age of the Down's syndrome subjects was 28 years (range 21-38), and their mean IQ was 28 (range 9-64).

Twenty-two control subjects also participated. Two gave brain stem recordings of unacceptable quality and one was rejected on the basis of left/right hearing asymmetry. The control group thus consisted of nineteen individuals drawn from UCLA students, hospital staff and volunteers. Their mean age was 28 (range 16-56).

Clicks (0.1 msec duration, 65 dB HL) were delivered through TDH-39 headphones. Stimulus repetition rate was 1/sec for the cortical ERPs and 20/sec for the brain stem ERPs. Blocks of 128 (cortical) or 2048 (brain stem) stimuli were delivered to left, right or both ears. With the exception of one Down's syndrome individual, it was possible to complete two repetitions of each stimulus condition. The EEG was recorded from a vertex electrode referred to the left mastoid. The ground electrode was on the forehead. Inter-electrode resistance was generally below 5K Ohms. EEG signals were conditioned by Grass P511 amplifiers. Cortical EEG activity from 1-100 Hz (3 dB down) was amplified with a gain factor of 50K; brain stem activity between 30 and 3 K Hz was amplified by 200 K. During the recording the subjects reclined on a bed located inside a sound attenuating room. An attendant remained with hospital residents at all times. Signals were averaged on line by means of a Nicolet 1170 computer. An averaging epoch of 500 msec was used for cortical recordings and an epoch of 10 msec for the brain stem recordings.

The main comparisons between the ERPs in the binaural condition and the sum of the ERPs in the monaural left and monaural right conditions (L + R). Latencies were measured for the N1, P2 and N2 components of the cortical response and for waves I-VI of the brain stem response. Waves IV and V were frequently difficult to separate so the IV-V "complex" was considered as one component. Amplitudes

were obtained for N1-P2 and P2-N2 of the cortical response. Amplitudes of the brain stem responses were measured from the peak waves I, II, III and IV-V to the immediately following trough, from the trough following wave III to the peak of IV-V and from the trough between waves V and VI to the peak of wave VI. Average values for the two replicates were analyzed by means of a 2 X 2 (retarded vs. non-retarded X binaural vs. monaural) repeated measures analysis of variance computed separately for each component and independent t-tests.

Results

The waveforms of one normal subject are shown in Fig. 1 for the short latency (A) and long latency (B) potentials. As illustrated here, certain components in each latency region were smaller in amplitude in the binaural than in the summed monaural conditions. Table I compares the mean amplitudes for each peak in the binaural and monaural conditions (upward arrows code amplitude measurements from trough to peak, downward arrows from peak to trough). The brain stem potentials showed a significant within-subjects effect ($F = 30.29$, $df = 1, 28$, $p < .01$) for the amplitude measured from the trough following wave III to the peak of wave IV-V. Similar patterns were observed for the N1-P2 ($F = 31.39$) and P2-N2 ($F = 43.79$) amplitudes. In no case was there a significant group X condition interaction. Hence the normal and Down's syndrome groups showed similar patterns of larger ERP amplitudes for the left-plus-right than for the binaural stimulation. Also shown in Table I is the percentage increase of $(L + R)/B$ for each ERP component. Overall, cortical ERPs show larger increases than brain stem ERPs.

Table II compares the peak latencies and amplitudes of the two groups under binaural stimulation. All the brain stem potentials had shorter latencies in the Down's syndrome group but the differences were significant only for waves II ($p < .05$) and III ($p < .01$). The cortical data, however, showed significantly longer N1 latencies for the Down's syndrome group ($p < .05$). The amplitudes of the retarded subjects were smaller for waves II ($p < .05$). The amplitudes of the retarded subjects were smaller for waves II ($p < .01$), III ($p < .01$) and V ($p < .05$).

Discussion of Experiment I

The comparison of the groups under binaural stimulation showed that the Down's syndrome individuals had brain stem latencies for waves I and II that were significantly shorter than the normal group. In addition, the Down's syndrome subjects had significantly smaller brain stem amplitudes for waves II, III and IV-V. These results are

TABLE I. COMPARISON OF BINAURAL AND LEFT

PLUS RIGHT AMPLITUDES (in μV)

	I↓	II↓	III↓	↑V**	V↓	↑VI	N ₁ -P ₂ **	P ₂ -N ₂ **
NORMALS: B	.19	.12	.27	.76	.83	.15	2.26	2.95
L + R	.18	.12	.30	.91	.89	.22	3.40	4.32
% (L + R)/B	(-5)	(0)	(+11)	(+20)	(+7)	(+47)	(+50)	(+46)
DOWN'S: B	.17	.05	.13	.62	.77	.12	2.38	3.04
L + R	.13	.05	.14	.72	.80	.14	3.67	4.49
% (L + R)/B	(-24)	(0)	(+8)	(+16)	(+4)	(+17)	(+54)	(+48)

TABLE II. COMPARISON OF BINAURAL ERPs FOR NORMAL (N=19)
AND DOWN'S SYNDROME (N=11) SUBJECTS.

A. LATENCY (in msec)

	I	II*	III**	V	VI	N ₁ *	P ₂	N ₂
NORMALS	1.77	2.93	3.90	5.86	7.50	87.6	151.0	248.9
DOWN'S	1.67	2.79	3.69	5.69	7.30	101.4	161.4	250.9

B. AMPLITUDE (in μV)

	I↓	II↓**	III↓**	↑V*	V↓	↑VI	N ₁ -P ₂	P ₂ -N ₂
NORMALS	.19	.12	.27	.76	.83	.15	2.26	2.95
DOWN'S	.17	.05	.13	.62	.77	.12	2.38	3.04

* $p < .05$ ** $p < .01$

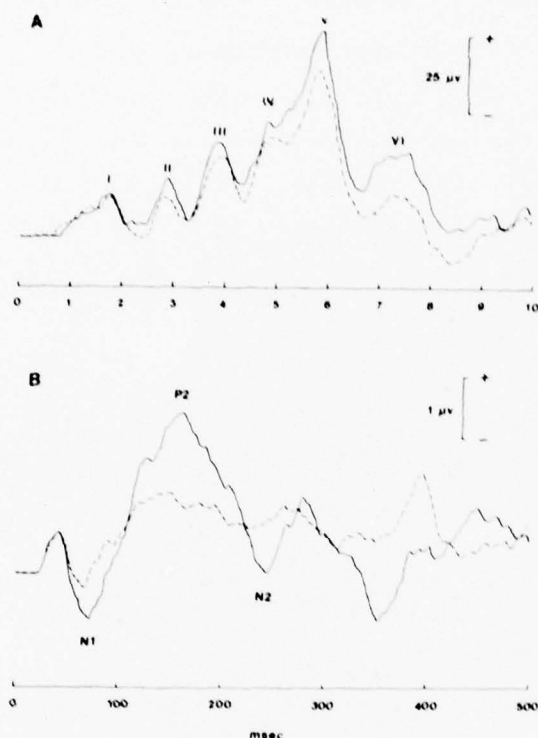


Fig. 1. Auditory evoked response of one normal subject to binaural (dashed line) and L + R monaural (solid line) stimuli. A. Short latency brain stem ERP. B. Long latency ERP.

similar to findings reported previously in our laboratory (Galbraith et al., in press), although in the present study significant effects were found for fewer waves.

The cortical ERPs showed a significantly longer N1 latency in the Down's syndrome group but no differences in amplitude. Several studies have previously reported longer evoked response latencies in Down's syndrome individuals (Bigum et al., 1970; Marcus, 1970; Gliddon et al., 1975). However, studies of Down's syndrome subjects also typically report significantly larger amplitudes as well (Barnet and Lodge, 1967; Bigum et al., 1970). Gliddon et al. (1975) showed that large evoked response amplitudes in Down's syndrome individuals occur primarily at higher stimulus intensity levels (in the visual system

at least). The lack of an amplitude differential in the current results might reflect the difference in stimulus modality or the lack of an optimal stimulus intensity. In view of the growing literature on the effects of attention on the amplitude of the vertex potential (Hillyard and Picton, 1978), it is also possible that previous reports reflect differential attention between the two groups as a function of stimulus intensity. Such effects are less likely in the auditory system since peripheral adjustment of the sensory mechanisms is not a factor. Comparisons of these late potentials are probably best made under conditions where independent information is available on the subject's psychological state (Sutton, 1969).

While binaural interactions might have been expected at the level of the superior olive (wave III) on the basis of the neurophysiological literature, the restriction of these effects to wave IV-V in both groups of adults studied here is consistent with previous investigations of the surface potentials in cats (Jewett, 1970; Huang and Buchwald, 1978).

The cortical data showed a significant binaural occlusive effect for both amplitude measures (N1-P2 and P2-N2). However, the size of the effect (in terms of the L + R/B ratio) was larger in the cortical ERPs than in the brain stem. It thus appears that the binaural occlusion increases from the level of the inferior colliculus (the probable generator of wave V) to the cortex. The amplitudes of wave VI are in line with this trend (Table I) although the difference between conditions was not significant at this level.

Despite the fundamental differences in the latency and amplitude characteristics of the ERP between the Down's syndrome and normal groups at all levels, the ERP reflections of binaural processing were nearly identical for the two groups. To the extent that the processes reflected here are involved in binaural analyses such as lateralization and localization, the data suggest that those aspects of information processing are essentially normal in the Down's syndrome individuals. This conclusion would be consistent with recent behavioral assessments of localization in the retarded (Heffner, 1977).

EXPERIMENT II: VISUAL ERPS AND PERCEPTUAL AND DECISION PROCESSES

As one proceeds to successively longer latency components, the dependence on stimulus parameters is reduced. Thus while the auditory far field responses are entirely stimulus bound, the N1-P2 component of the vertex potential is affected both by stimulus and cognitive variables, and the endogenous components N2 and P3 are almost completely dependent on the subject's psychological reaction

to the stimuli. This experiment sought to determine whether separate contributions of perceptual and cognitive factors to the visual ERP would differentiate between retarded and normal adults.

Typically the endogenous components are elicited in tasks that require the subject to count or otherwise keep track of certain stimulus events. Under these conditions unexpected events reliably evoked endogenous N2 and P3 components in addition to the exogenous components evoked by all stimuli. While procedures such as the counting task are simple and effective with normal subjects, they must be modified to be within the capabilities of our target population. The procedure we have adopted does not require that the subject make difficult decisions about the stimuli, or even to discriminate the different events, and is suitable for all but the very lowest functioning individuals.

Method

Three visual stimuli occurred in random order in each block of trials. One was presented frequently ($p = .80$) and the other two were presented rarely ($p = .10$). One of the rare stimuli was a red circle on a white background and was designated as the target. The retarded subjects were taught to associate the target stimulus with a token reward by requiring them to say "token" to each occurrence of the target if they were verbal or to point to the stimulus if they were not. If no response was made the subject was prompted. Tokens were given for correct response and were exchanged later for food or other rewards. Nonretarded subjects tested in the same procedure pressed a button in response to the target stimulus. The purpose of the verbal or nonverbal response to the target was to keep the subject's attention on the visual display.

The nontarget stimuli, which did not require a response, provided the major experimental data since the ERPs to these stimuli were free from contamination due to motor responses. (Since no emphasis was placed on speed of response and most responses to the targets occurred beyond the one-second averaging epoch, the target ERPs were also relatively free of artifact.) The frequent stimulus was always a dim flash (1 fTL). In separate blocks the rare nontarget stimulus was either a small increase in stimulus intensity (11 fTL, the "small increment" condition) or a large increase in intensity (110 fTL, the "large increment" condition). All nontarget stimuli were 200 msec in duration. The target stimuli remained on the screen until a response was made. Stimuli were presented via a Kodak Carousel projector at the rate of one per second in blocks of 80 stimuli. Half of the subjects were given the large increment condition first, and the other half were given the small increment condition. Each condition contained three blocks of stimuli.

Thirty retarded subjects of mixed diagnosis and thirteen normal subjects participated in the experiment. The ages of the retarded subjects ranged from 13 to 53 (mean = 26), and their IQs from 6 to 69 (mean = 35). The ages of the normal subjects ranged from 19 to 55 (mean = 25). The normal subjects were non-paid UCLA students and staff volunteers. The data of one retarded and one normal subject were excluded due to equipment malfunctions.

Electrodes were placed at Fz, Cz and Pz referred to the right mastoid. The left mastoid was used as ground, and the EOG was measured from above the right eye to the outer canthus. All trials with large eye movements were excluded from the average. The data of one retarded subject were excluded due to excessive eye movement. During testing the retarded subject's behavior was monitored, and data from periods of inattention or excessive movement were rejected. For most subjects such periods were rare. The EEG was amplified with Grass P511 amplifiers (.1-100 Hz), digitized and stored on magnetic tape for off line averaging and analysis.

Results

Fig. 2 shows the ERPs to the rare and frequent nontarget stimuli for three retarded and three normal subjects in the large increment condition. For both the retarded and normal subjects the ERPs to the frequent stimuli (solid lines) consist of the N1 and P2 components while the ERPs to the rare stimuli (dashed lines) also contain the endogenous N2 and P3 components.

As would be expected of the exogenous components, N1-P2, amplitude increased as a function of increasing intensity of the three nontarget stimuli ($F = 52.7$, $df = 2,76$, $p < .01$; Fig. 3). There was no significant difference in the N1-P2 amplitudes of the retarded and normal subjects and no significant interaction with stimulus intensity.

For the N2-P3 component there was no main effect on amplitude of the type of rare stimulus (large increment flashes, small increment flashes and targets); however, N2-P3 amplitudes were smaller in the retarded (mean = 13.9 μV) than in the normals (mean = 20.4 μV ; $F = 11.57$, $df = 1,38$, $p < .01$). There was also a significant interaction between stimulus and group effects ($F = 7.0$, $df = 2,76$, $p < .01$); the N2-P3 amplitude difference between groups was greater for the target stimuli than for either of the other rare stimuli.

Fig. 4 shows the mean latencies of the components averaged across the three types of rare stimuli. While N1 latency did not differ between the normal and retarded subjects ($F = .1$, $df = 1,38$), significant latency differences were found for P2, N2 and P3 ($F = 14.86$, 22.65 and 10.53 , respectively, $df = 1,38$ and $p < .01$ in each case).

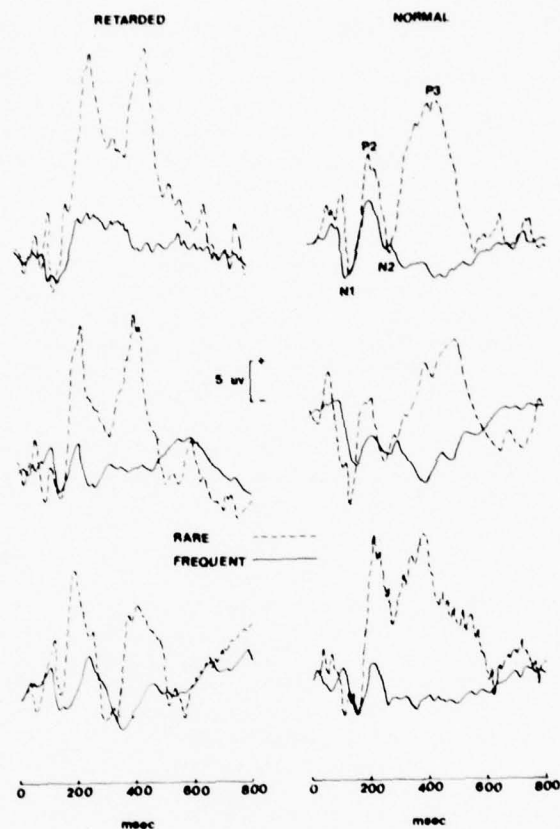


Fig. 2. Visual evoked responses of three retarded and three normal subjects in the large increment condition.

Although N1 was of normal latency for the retarded group as a whole, one subset from the retarded group did have prolonged N1 latencies. Eight of the retarded were reported by the direct care staff as having visual difficulties. Significantly more of these individuals had N1 latencies that were greater than one standard deviation above the mean for the normal subjects ($\chi^2 = 5.62$, $p < .01$). Similar analyses of the effect of visual deficits on the latencies of the later peaks showed no significant differences.

The mean latency of the P3 to the nontarget rare stimuli decreased by about 40 msec from the small increment condition to the large increment condition for both the retarded and the normal sub-

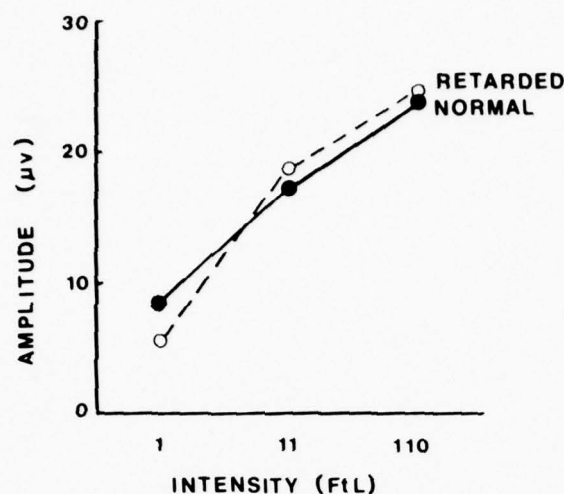


Fig. 3. N1-P2 amplitude as a function of the intensity of the non-target stimuli.

jects, and P3 latency was about 50 msec longer in the retarded than in the normals in each condition (Fig. 5). The P3 latency of the retarded to the large increment was thus about the same as the P3 latency of the normals to the small increment. There were no significant differences between normal and retarded in the scalp amplitude distribution of the P3s to any of the rare stimuli. The mean amplitudes across all rare stimuli were 12.6, 13.9 and 12.8 μ V at Fz, Cz and Pz for the retarded and 16.9, 20.4 and 16.1 μ V for the normal subjects.

Discussion of Experiment II

The main difference in the visual ERPs of the retarded and nonretarded subjects was in the endogenous components evoked by the rare events. These components were of longer latency and smaller amplitude in the retarded than in the normal subjects. Since P3 latency primarily indexes the speed of a perceptual decision (Ritter et al., 1972; Ford et al., 1976; Squires et al., 1972, Kutas et al., 1977) the latency data suggest that the information processing of the retarded is characterized by slower perceptual recognition and decision processes. Since P3 amplitude is influenced by a subject's expectancies and by his/her memory for events in the prior sequence of events (Squires et al., 1976), the smaller than normal P3 amplitudes of the retarded subjects may be the result of deficiencies in expectancy formation or in memory processes, both of which have been implicated in behavioral studies of retardation (Kirby et al., 1977).

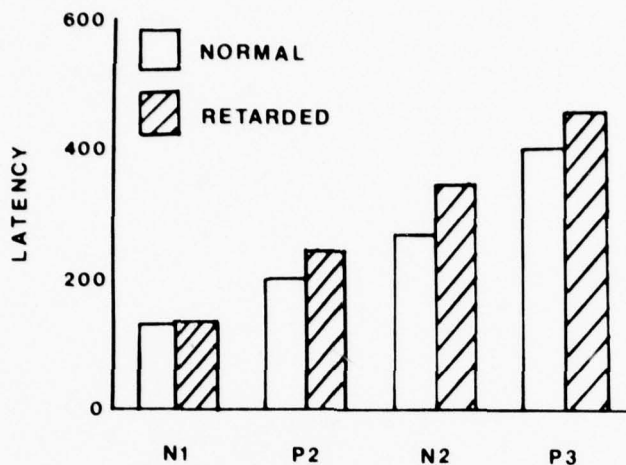


Fig. 4. Peak latencies of the major ERP components averaged across the three rare stimuli.

The ERP differences shown here between the retarded and the normal subjects cannot be readily attributed to differences in sensory acuity since the latency and amplitude of the exogenous N1 component did not differ between the two groups. The use of N1 latency as a measure of sensory magnitude is supported by the delayed N1s found for those retarded subjects with reported visual problems. That N1 could be delayed in these individuals without a concomitant slowing of decision processes, indexed by P3 latency, is consistent with the data of Squires et al. (this volume) who found that in normal subjects decreasing the intensity of auditory stimuli produced a delayed N1 but had no effect on P3 until both the rare and frequent stimuli were within 15 dB of threshold. Apparently P3 latency is determined by the perceptual recognition of stimulus differences rather than by absolute stimulus intensity.

As a whole these data suggest that the visual information processing of the retarded is characterized primarily by deficits in the higher cognitive functions reflected in the endogenous potentials. This pattern of normal exogenous potentials and abnormal endogenous potentials is typical of populations with diminished mental functions such as the demented and the aged (Squires et al., this volume; Goodin et al., in press) as well as the developmentally immature (Squires et al., this volume; Goodin, 1978) and the hyperkinetic (Pritchard et al., 1976). To determine whether or not the ERP abnormalities of these groups actually reflect the same functional deficiencies, more detailed experiments need to be performed to parcel out the contributions of short- and long-term

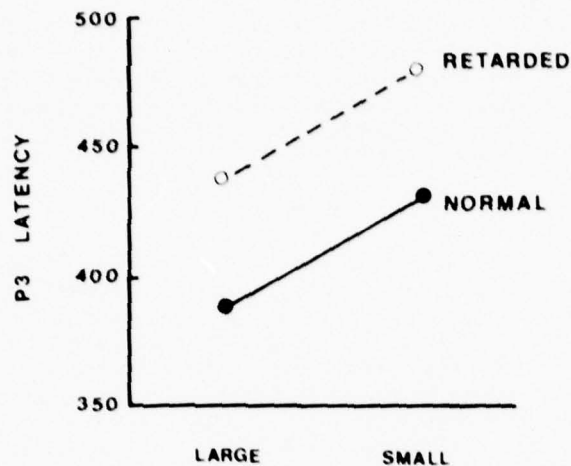


Fig. 5. P3 latency as a function of the intensity difference between rare and frequent stimuli.

memory, perceptual and other cognitive factors. Many ERP techniques for making such distinctions have already been developed in research with normal adult subjects and the field is making continuous progress in this direction (Donchin et al., in press).

CONCLUSION

It is increasingly evident that a high degree of analytical specificity can be obtained from components of the ERP. Thus the sequence of potentials occurring within 10 msec following a brief auditory stimulus reflect quite specific processes within the auditory relay nuclei and pathways of the brain stem. Such potentials reflect only stimulus characteristics and are not altered by attention, sleep, etc. At the other extreme the long latency potentials are known to reflect both endogenous and exogenous factors but more generally at a higher (i.e., cortical) level. Not surprisingly, the clarification of these endogenous properties often requires special experimental paradigms.

Neuroanatomical and neuropathological studies indicate that mentally retarded individuals suffer from disturbances in neural organization throughout the extent of the brain, from brain stem to cortex. We sought, therefore, to utilize the ERP as a means of elucidating possible differences in neural organization between mentally retarded and nonretarded individuals. Our results showed

instances where there were no differences. However, certain parameters were significantly different in both the brain stem and cortical ERPs. We feel, therefore, that the ERP has great utility in providing meaningful information about the functional integrity of the mentally retarded nervous system.

SUMMARY

Both the long- and the short-latency auditory evoked responses were recorded in a group of Down's syndrome retarded individuals and in a group of normal controls to assess binaural auditory information processing. Previous studies in animals and normal humans show that amplitudes are reduced during binaural stimulation as compared to the sum of monaural left-plus-right ear stimulation. The current results showed that Down's syndrome subjects had shorter BAER latencies and reduced amplitudes. Their long latency potentials had normal amplitudes, but longer than normal latencies. Despite these differences in the auditory evoked potentials, however, the degree of amplitude decrement produced by the binaural stimulation was similar in the Down's syndrome and normal groups. It, therefore, appears that the processing of simultaneous input from the two ears is not degraded in Down's syndrome individuals insofar as that processing is reflected in the potentials investigated. The visual evoked responses for a group of retarded adults of mixed diagnoses were compared to those of a group of normal adults. The primary differences in the ERPs of the two groups were found in the endogenous components, N2 and P3, suggesting diminished perceptual recognition and decision making processes in the retarded individuals. The earlier N1 component was abnormal only in a subset of retarded individuals with known deficits in visual acuity. The N2 and P3 components of this subset did not differ from the retarded group as a whole. These results indicate that the exogenous (N1 and P2) and endogenous (N2 and P3) components of the visual response can be used to differentiate between sensory and cognitive deficits in the visual information processing of the retarded.

ACKNOWLEDGEMENTS

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ANATOMICAL AND PHYSIOLOGICAL ORIGINS OF AUDITORY BRAIN STEM
RESPONSES (ABR)

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The development of far field recording techniques to measure the activity of the auditory pathway in its course from the cochlea to the cortex has had important clinical applications. In man there are up to seven vertex positive waves that occur in the first ten msec after a click signal (Fig. 1). The largest of these components, designated variously as the IV-V complex, 4a and 4b, or N4 and N5, is usually 0.5 μ V in amplitude and occurs at a latency of 5.6 - 6.0 msec for a 65 dB (H.L. re normal) click. Since the components of the auditory brain stem responses (ABR) change in latency in an orderly manner with signal intensity (Fig. 1) the measure can provide objective definition of hearing threshold in difficult-to-test subjects such as newborn infants or mentally impaired patients (Davis and Hirsch, 1977; Hecox and Galambos, 1974; Mokotoff et al., 1977; Shulman-Galambos and Galambos, 1975; Sohmer and Feinmesser, 1973; Starr et al., 1977; Yamada et al., 1975). The ABR evoked by clicks primarily reflects high frequency hearing capacities since it depends on the activity of the basilar or high frequency end of the cochlea. However, there are several methods under evaluation that will enable the ABR to serve as a reliable measure of hearing threshold across a wide range of signal frequencies; these include the use of filtered clicks (Davis, 1976) and narrow band masking noise (Don and Eggermont, 1978).

The expectation that each component of the ABR represents the activity of one of the nuclei along the brain stem auditory pathway (Jewett, 1970; Lev and Sohmer, 1970) has obvious relevance for the evaluation of neurological disorders. A large body of clinical data has now been collected that show correlation between alterations in the ABR and various brain stem lesions (Chiappa et al., in press; Robinson and Rudge, 1977; Starr, 1976, 1977; Starr and Achor

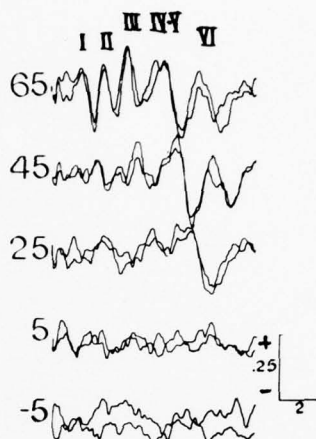


Fig. 1. Auditory brain stem responses from a normal human adult. Recording was made between vertex (Cz) referenced to the earlobe ipsilateral to the click stimulus. The intensity of the click in dB H.L. re a jury of normal subjects is to the left of each response. Duplicate averages were obtained of each intensity. Note the latency shift of the components as signal intensity is lowered. This subject did not show a Wave VII.

1975; Starr and Hamilton, 1976; Stockard et al., 1977; Stockard and Rossiter, 1977; Thornton and Hawkes, 1976).

Two types of changes in the ABR occur with central nervous system lesions in man. The first is a loss or marked attenuation of components of the ABR; the second is a prolongation in latency between the various ABR components, in which case there is abnormal "central conduction time". Since absolute amplitudes of the components of the ABR can vary considerably among normal subjects, due to the low amplitude of the ABR relative to amplifier "noise" or other biological signals such as the electroencephalogram (EEG) or electromyogram (EMG), we have suggested that amplitude ratios of various components can be a useful index of abnormality. In particular, Wave V is usually larger than Wave I ($V/I > 1$) to signal intensities of 60 dB H.L. re normal or less (Chiappa et al., in press; Rowe, 1973; Starr and Achor, 1975).

The measure of central conduction times was developed for neurological evaluations because the absolute latency of all of the components will be affected by middle ear or cochlear functions, whereas the interpeak latencies are relatively independent of both

click intensity and hearing loss (Rowe, 1973; Starr, 1977; Stockard, and Rossiter, 1977). The time difference between Waves I and V is commonly employed, and values above 4.4 msec are considered to be abnormal (> 2 S.D. above normal). Variables such as body temperature (Stockard et al., 1978) and depressant drugs (Squires et al., 1978) can prolong central conduction times, but this measure will exceed normal values only when these factors are extreme.

From a survey of the clinical data (Starr, 1978) it appears that lesions of the thalamus or cortex are not associated with changes in the ABR. The report that Waves VI and VII were abolished in a patient with a thalamic tumor (Stockard and Rossiter, 1977) is of limited use since these components may also be absent in normal subjects (Chiappa et al., in press; Rowe, 1978). Lesions of the midbrain are associated with a loss or prolongation in latency of components beginning with Waves IV and V. Lesions of the pons affect the ABR beginning with component III. Lesions of the eighth nerve may be associated with a loss of the entire ABR or prolongation in the latency of components after Wave I. Wave I may also be increased in width with tumors that compress the eighth nerve (Terkildsen et al., 1977). The changes in the ABR in these clinical situations suggest that the generators of the various components of the ABR may be as follows: Wave I - the eighth nerve; Wave III - the pons; Waves IV and V - the midbrain. Waves II, VI and VII occur with sufficient variability in normal subjects making a definition of their generators from clinical-pathological studies uncertain.

The types of lesions encountered in clinical situations usually extend beyond a single auditory structure and, in addition, have remote effects on other parts of the brain stem from pressure or edema. The results of using the ABR in the clinic provides an impetus for further experimental studies in animals to clarify in precise detail the generator sites for the various components.

Two types of experimental studies have been performed in animals to define the anatomical bases of the ABR. The first method relies on a correlation between the latency of evoked potentials or single units recorded in particular brain stem auditory structures with the components of the ABR recorded from the scalp (Achor, 1976; Huang and Buchwald, 1977; Jewett, 1970). The second method relies on changes in the ABR that accompany the destruction of portions of the auditory pathway (Buchwald and Huang, 1975; Lev and Sohmer, 1970). These studies have been interpreted as indicating that certain components of the ABR are generated by a single auditory structure, but there may be disagreement as to the identity of that structure. For instance, Jewett (1970), using depth and surface evoked potentials in the cat, found large amplitude fields in the inferior colliculus at the time of Wave IV, whereas Buchwald and Huang (1975) found that ablation of the inferior colli-

culus in the cat was not associated with any changes in Wave IV. The study by these last authors, which involved making sequential transections of the brain stem in cats, suggested that Wave I originates from the eighth nerve, Wave II from the cochlear nucleus, Wave III from the superior olive, Wave IV from bilateral pathways in the pons and Waves V and VI (both of which are quite small and variable in the cat) from the inferior colliculus. There are some obvious differences between the clinical material in humans and the results from cats, the major one being the identity of the generators for Waves IV and V.

We have been investigating the origins of the ABR in anesthetized cats using both depth recordings and the effects of discrete brain stem lesions. An examination of the evoked potentials recorded from several of the auditory structures (Fig. 2) shows that each may extend for many msec, and therefore several sites can be active simultaneously. Thus a causal relationship between activity in one brain stem structure and the far field occurrence of one component of the ABR is unlikely.

In our experiments we made a detailed analysis of the evoked potentials every two millimeters throughout the brain stem. This relatively fine-grained analysis provided a detailed spatial estimate of the distribution of potential fields in the brain stem

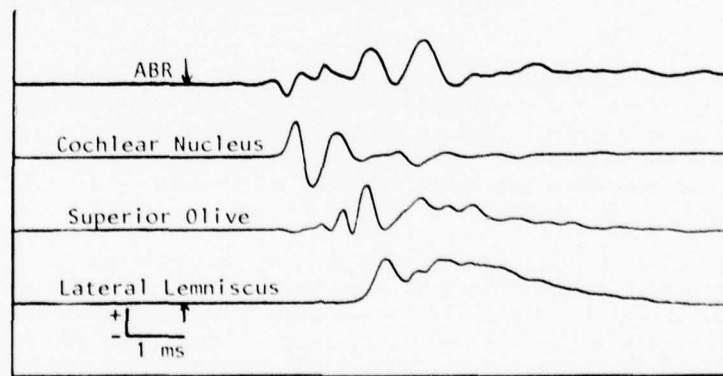


Fig. 2. Auditory brain stem responses (ABR) recorded from the scalp referenced to the neck of an anesthetized cat (top trace) compared with recordings from several auditory brain structures also referenced to the neck. The amplitude calibration for the ABR is 10 μ V and for the depth recordings, 500 μ V. The click stimulus was presented at the arrow through stereotaxic hollow ear bars. Note that the potentials evoked in the auditory brain stem sites persist for many msec.

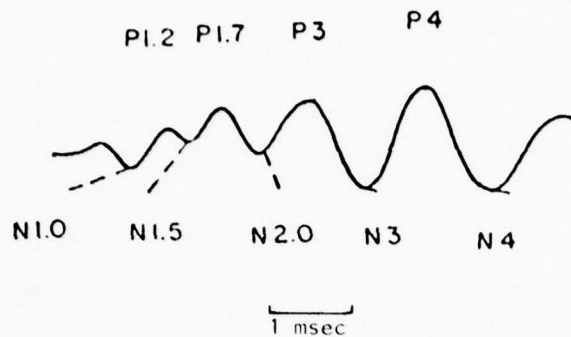


Fig. 3. Auditory brain stem potentials recorded from the anesthetized cat as in Fig. 2. The time base has been enlarged and the components labeled for reference to Tables I and II.

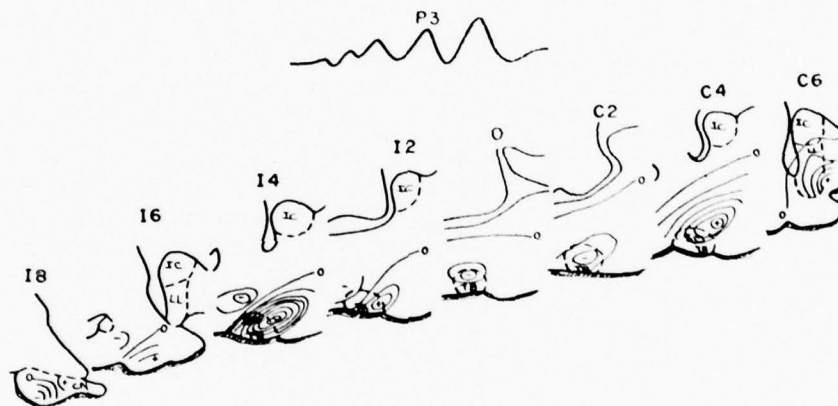


Fig. 4. An isopotential map of the brain stem of the cat at the peak of component P3. There are eight sagittal sections onto which are traced the isopotential contours. The sections begin in the brain stem ipsilateral to the stimulated ear and proceed in 2 mm steps across the brain stem. Rostral is to the right of each section. The letters above each section refer to the plane of the section (I8 is ipsilateral 8 mm from the midline, I6 is ipsilateral 6 mm, etc., 0 is the midline and C refers to contralateral sections). There is no section at C8 because of the absence of any fields in the contralateral cochlear nucleus. The zero isopotential plane (0) is indicated in each section and each line represents a 200 μ V change. The polarity of the field, i.e., positive (+) or negative (-) is also indicated. Note that significant potential fields are present in almost every section of the brain stem at the peak of P3.

at the time of occurrence of each peak and trough of the ABR (Fig. 3). Fig. 4 shows one of the isocontour maps that derives from the analysis of the distribution of potential fields throughout the brain stem at the time of occurrence of one of the components, P3. It is obvious that at this instant in time there are high amplitude fields present throughout the brain stem from cochlear nucleus to colliculus. These fields, moreover, are not stationary but show rapid movement through the brain stem within a few hundred micro-seconds. Fig. 5 includes the potential maps from a single sagittal section of the brain stem involving the contralateral inferior colliculus and lateral lemniscus at the peak of P3 and 100 msec both prior to (-100) and after (+100) its occurrence. Note the movement of the fields from the pons up to the colliculus in this short time span.

Quantification of the amplitudes of the potentials in the various auditory nuclei and tracts of the brain stem at the time of each of the components of ABR revealed that more than one site had high amplitude fields at the time of each of the components. Table I contains the results from this analysis in four cats. For each component of the ABR in each of the cats the amplitude of the potential field in a brain stem auditory structure was expressed as a percentage of the maximum field found anywhere in the brain stem at that instant in time. The positive and negative fields were averaged separately, and those fields that were 40% or more of the maximum field found anywhere are noted by an asterik and arbitrarily considered a "major" contributor to the ABR component. A single source (VIII N/CN) can be defined for the initial three components (N 1.0, P 1.2, N 1.5). Thereafter significant voltage fields (> 40% of maximum) occur in several of the auditory structures at the time of each of the ABR components. For instance, at the time of P 3.0 there are at least four sites with significant potential



Fig. 5. An isopotential map of one plane of the brain stem of the cat (contralateral 6) through the inferior colliculus and lateral lemniscus at the peak of P3 (middle trace) and 100 μ sec before (-100) and after (+100) this component. Note the movement of the field from the pons up to the inferior colliculus in this short time span. The description of the contour maps are in Fig. 4.

Table I. Potential fields in the brain stem auditory pathway expressed as a percent of the maximum field anywhere in the brain stem at the time of occurrence of each of the ABR components (N = 4 cats).

		ABR COMPONENT									
		Positive Fields									
		N 1.0	P 1.2	N 1.5	P 1.7	N 2.0	P 3.0	N 3	P 4	N 4	
VIII N/CN		95*	80*	50*	32	75*	20	22	15	10	
(I) SO		0	0	0	8	60*	55*	35	40*	7	
(I) LL		0	0	0	0	0	0	0	40*	0	
(I) IC		0	0	0	0	0	0	0	0	0	
TB		0	0	10	63*	65*	58*	38	0	15	
(C) SP		0	0	0	0	48*	85*	45*	30	52*	
(C) LL		0	0	0	0	0	40*	38	42*	8	
(C) IC		0	0	0	0	0	0	0	0	15	
		Negative Fields									
VIII N/CN		15	75*	95*	85*	35	30	8	0	33	
(I) SO		0	0	0	7	40*	38	52*	48*	5	
(I) LL		0	0	0	0	0	0	0	0	47*	
(I) IC		0	0	0	0	0	0	0	0	0	
TB		0	0	7	0	10	0	0	60*	0	
(C) SO		0	0	0	9	30	43*	92*	85*	55*	
(C) LL		0	0	0	0	21	0	68*	24	72*	
(C) IC		0	0	0	0	0	0	0	0	0	
		IC inferior colliculus nucleus									
		TB trapezoid body									
		(I) ipsilateral to acoustic stimulus									
		(C) contralateral to acoustic stimulus									

* denotes fields > 40% of maximum anywhere in brain stem

VIII N/CN eighth nerve/cochlear nucleus

SO superior olive nucleus

LL lateral lemniscus

fields: the ipsilateral and contralateral superior olives, the trapezoid body and the contralateral lemniscus. There did not appear to be any regular correlation between the polarity of the brain stem fields and the polarity of the far field components. Finally, the inferior colliculus did not have high amplitude fields at the time of the occurrence of the ABR through component P4. Thus the results of this potential field analysis suggest that for each component of the ABR (beginning with P 1.7) there is more than one auditory brain stem structure making a significant contribution to its generation. Moreover not every auditory structure appears to participate in the generation of the ABR.

There are several weaknesses in this type of potential field mapping study. First, the definition of a high amplitude field in the brain stem does not assure that the field is reflected on the surface. Second, the mapping does not take into account such variables as "closed" versus "open" fields and inhomogenities in current movements through the brain. Finally, the requirements for multiple electrode penetrations to obtain these maps must have disrupted "normal" brain stem functions. However, in spite of these limitations the major conclusion that the generators of most of the ABR components involve several auditory structures is quite apparent.

We then carried out a second series of experiments making discrete electrolytic lesions in various auditory brain stem structures and assessing the changes in the ABR. The experiments were carried out in anesthetized cats. The major effect of these acute electrolytic lesions was to attenuate the amplitude of the ABR and to have little effect on latency. Fig. 6 shows that an extensive unilateral lesion and a smaller contralateral lesion in the central nucleus of the inferior colliculus has no effect on the ABR. This result corresponds to the conclusions of the field mapping studies. In contrast, a lesion in the ventral cochlear nucleus (Fig. 7) affected all the components beginning with P 1.7. Table II contains a list of the changes in the amplitude of the ABR components with lesions at different levels of the auditory brain stem pathway. The data for each level is derived from a single animal and were chosen because the animal demonstrated maximum effects from the lesion among the animals studied.

A complete lesion of the eighth nerve attenuated all neural components. The remaining events detected in scalp recordings were cochlear microphonics. A lesion of the ventral cochlear nucleus (VCN) that destroyed approximately 50% of the structure caused an attenuation of all components of the ABR (40-76%) beginning with P 1.7 to an ipsilateral stimulus. A partial lesion of the ventral acoustic striae (VAS) just medial to the cochlear nucleus attenuated P3, and P4 and N4 to ipsilateral stimulation. N3 was not affected. A lesion of the superior olivary nucleus (SO) that also transected

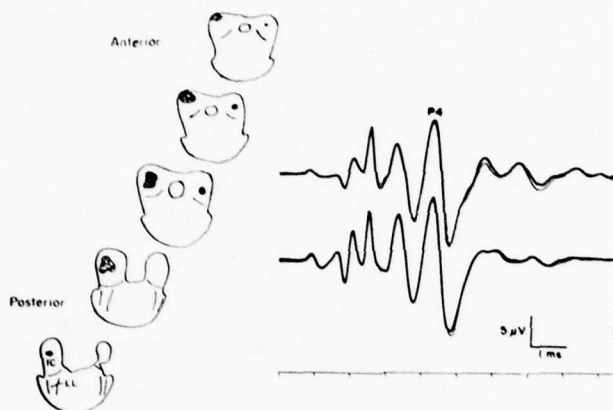


Fig. 6. Auditory brain stem responses from stimulation of each ear (top and bottom traces) from a cat before (faint lines) and after (dark lines) an electrolytic lesion of the inferior colliculus. The extent of the lesions are shown in the figure. One of the lesions destroyed approximately 50% of the nucleus unilaterally. There was not change in the ABR.

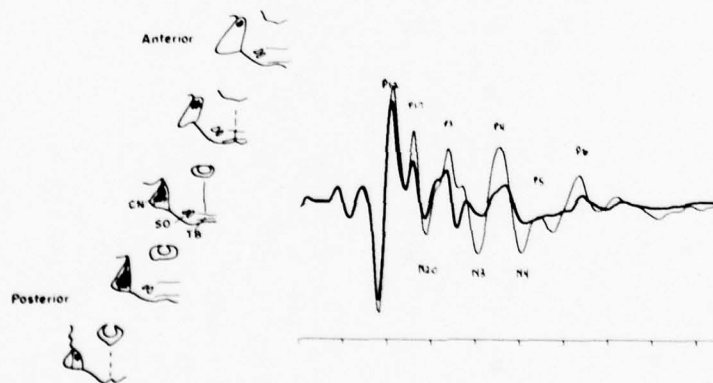


Fig. 7. Auditory brain stem responses from a cat before (light line) and after (dark line) a lesion of the ventral cochlear nucleus. Note that components beginning with P 1.7 are markedly attenuated without a latency shift. The amplitude decrements in P 1.2 and N 1.0 are less than 10% and cannot be distinguished from normal variability. The amplitude scale of the abscissa is 1.0 msec.

Table II. The decrease in amplitude of the ABR components (expressed as a percentage change) with particular lesions.

ABR COMPONENT	VIII N*	VCN*	VAS*	LESION SITE				TB	LL**	DCN/DAS/IC
				I	I	C	SO			
P 0.8 - N 1.5	100	0	0	0	0	0	0	0	0	0
P 1.7	100	40	0	0	0	0	0	20	0	0
N 2.0	100	48	0	0	0	0	0	0	0	0
P 3.	100	40	38	95	95	36	37	0	0	0
N 3.	100	74	0	90	34	89	78	44	0	0
P 4	100	76	44	95	42	33	32	0	0	0
N 4	100	64	22	74	63	50	41	29	0	0

* Effect only on ABR to ipsilateral stimulation

** Effect only on ABR to contralateral stimulation

o These components shift in polarity but do not change in amplitude if measured from the peak of

P 1.7

VIII N eighth nerve
VCN ventral cochlear nucleus
VAS ventral acoustic stria
SO superior olive nucleus
TB trapezoid body
LL lateral lemniscus
DCN dorsal cochlear nucleus
DAS dorsal acoustic stria
IC inferior colliculus
I ipsilateral
C contralateral

50% of the trapezoid body fibers ventral to the nucleus severely attenuated (> 75%) the components of the ipsilaterally evoked ABR from P3 on. While P3 of the contralaterally evoked ABR was almost totally abolished (95%), the subsequent components (N3, P4, N4) of the contralaterally evoked ABR were only partially affected (34%, 42% and 63%, respectively). Thus a unilateral lesion of the superior olive nucleus (SO) can have equivalent effects on P3 evoked from stimulating each ear but markedly asymmetrical effects on P4. The difficulty with interpreting the superior olivary lesions is that they also invariably impinged on the trapezoid body (TB). A lesion of this latter structure in the midline that did not destroy the superior olivary had fairly comparable effects on the ABR evoked from ipsilateral or contralateral stimulation. The effect began with P 1.7 but was maximal at N3. Finally a lesion of the lateral lemniscus (LL) affected the ABR evoked by contralateral stimulation but was limited to N3 and N4 and spared P4.

A synthesis of the results from the lesion experiments suggests that N4 is generated in both the superior olive and the lateral lemniscus; P4 is generated in bilateral pathways close to the superior olives; N3 is generated in both the lateral lemniscus and the superior olive; P3 is generated primarily in the superior olives; N 2.0 and P 1.7 are generated primarily in the cochlear nucleus, and all other components originate in the eighth nerve.

We emphasize caution in transferring the ABR results derived from electrolytic lesions in animals to the human clinical experience. First, in several animals which were allowed to recover after the lesion the large amplitude changes in the ABR noted acutely were much less prominent when recordings were made in subsequent weeks. It is likely that the lesions may have had acute transient effects on brain stem structures remote from the electrode tip due to physiological factors (diaschisis), or even to vascular or edematous complications.

The prominent change in central conduction times of the ABR described in patients with disorders of brain stem function did not occur with the acute electrolytic lesions in these animal experiments. Certainly the types of pathological processes in humans (tumors, demyelinating disorders, edema, infarcts from vascular diseases) must have vastly different pathophysiological effects on neural processes than the electrolytic lesions employed here. Moreover, we suspect that amplitude changes of up to 40%, as defined in the ABR in these animal studies, would probably not be discernible as abnormal in man simply because the amplitude of the ABR is notoriously variable in man. Also, it is rare that both "before" and "after" records are available from humans; consequently, abnormalities must be defined on the basis of group data. The ABR in the cat, however, is more than forty times greater in amplitude, resulting in a marked

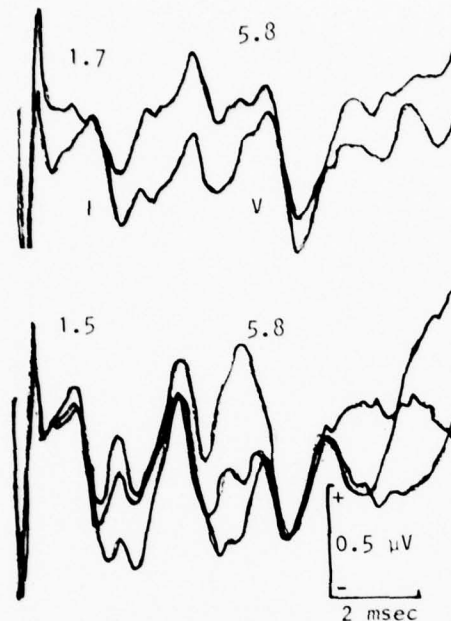


Fig. 8. Auditory brain stem responses from monaural stimulation of the right ear (upper) and left ear (lower) in a patient with a tumor of the tectum of the midbrain. Waves I and V are labeled. Note that the latency of the components are normal as were central conduction times ($I-V < 4.4$ msec). The only finding vaguely suggestive of an abnormality is that the amplitude of Wave V is less than I in two of the three responses from stimulating the left ear. At the time of this recording the patient was confused (obstruction of the aqueduct of Sylvius producing hydrocephalus), with a paralysis of upward gaze.

improvement in signal/noise relationship and allowing the absolute amplitude measures to be reliable.

To demonstrate that the animal studies are relevant to the clinical situation, we have encountered instances of lesions of the inferior colliculus in man without abnormalities of the ABR. Fig. 8 is from a patient who died with a tumor restricted to the tectum of the midbrain (the inferior and superior colliculus) without pressure or edema in the tegmentum of the brain stem. The ABR was normal throughout the two years the patient was observed. This result supports the animal studies in which lesions of the inferior colliculus did not affect the ABR. It is likely that the tegmentum of the midbrain coupled with the pons provide the major generator

sites for the components designated as III and IV-V in man. Furthermore attention should be paid to the vertex negative components in man since certain lesions in the animal studies (lateral lemniscus) had predominant effects on these troughs.

The ABR is an encouraging example of the clinical relevance of evoked potential and neurophysiological research. Its successful application has been based on a relatively clear understanding of peripheral and central auditory physiology and the ability to transfer this knowledge to the human condition.

SUMMARY

The generation of auditory brain stem responses was examined in anesthetized cats by using a field analysis of the potentials evoked every 2 mm in the brain stem to click stimuli. These field maps were correlated with the peaks and troughs of the scalp recorded auditory brain stem responses. The first three components (P 0.8, N 1.0 and P 1.2) appear to be generated in the eighth nerve. The remaining components, except for N4, are associated with large amplitude fields in two or more separate sites along the classical auditory brain stem pathway. Acute and chronic electrolytic lesions in portions of the auditory brain stem pathway in cats showed that discrete lesions may effect more than one component of the auditory brain stem responses. However lesions in the inferior colliculus, the dorsal cochlear nucleus and the dorsal acoustic striae may have no effect on brain stem responses. The lesions usually decreased the amplitudes of the evoked potentials and had little or no effect on latencies. All of these results suggest that the generation of auditory brain stem response cannot be attributed to a one-to-one relationship between a particular component and a particular site in the auditory pathway but rather reflect a complex interrelationship between the various structures.

ACKNOWLEDGEMENTS

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COLOR EVOKED POTENTIALS: CORTICAL AND SUBCORTICAL ELEMENTS

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In our work with responses to colored stimuli it was possible to identify specific components of the evoked waveforms as being related to three basic processes tentatively referred to as red, green and blue processes. This was achieved by selectively sensitizing the eyes with light which was passed through a variety of limited spectrum filters while presenting flashes obtained with standard red, green and blue filters.

In the original report on this work (White et al., 1977) the results of using a number of background colors were presented, a method which made it possible to detect trends in the waveform that indicated the nature of the underlying processes. The major results of that earlier work can be summarized by two sets of evoked waveforms, one representing red flashes against a blue-green background and the other being blue flashes against a yellow background. Both are new data obtained from one of the subjects studied in the earlier work.

Fig. 1 shows the subject's responses to flashes of red light (Wratten filter #92) of constant intensity under increasing levels of blue-green lights. The voltage values refer to the settings on a rheostat in series with the 60 watt tungsten bulb used to produce the background light.

The waveform for the in-dark condition (0 volts) is dominated by three positive peaks in the 100-200 msec time period. The waveform for the highest level background exhibits only two positive peaks in that time range. At intermediate background levels critical changes occurred. As the background level was increased the second peak moved forward in time from its original 150 msec position and

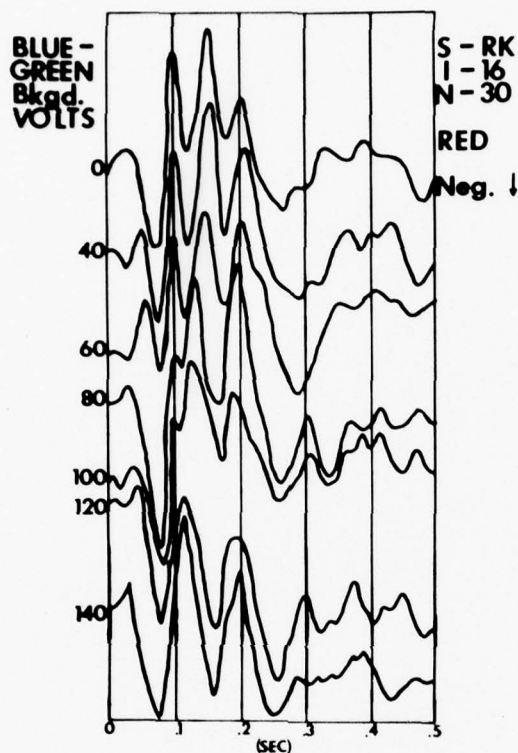


Fig. 1. Responses of a subject to red flashes upon a blue-green background. Montage: Oz to linked earlobes.

merged with the first peak, having a final latency of about 120 msec. The first peak now appeared as a shoulder on the leading edge of the combined positive element. With other backgrounds where higher intensities are possible (e.g., white or yellow) the second peak is much reduced in amplitude, finally appearing as a shoulder on the trailing edge of the first peak.

It is to be noted that the first peak did not change its latency as the background level was increased. This is also true for the third peak (180-200 msec), which is such a dominant feature of the high background response. On the basis of the responses obtained with the various background colors and the red flash stimuli, it was concluded that the first and third peaks (about 100 and 180 msec, respectively) are components related to the red color processes.

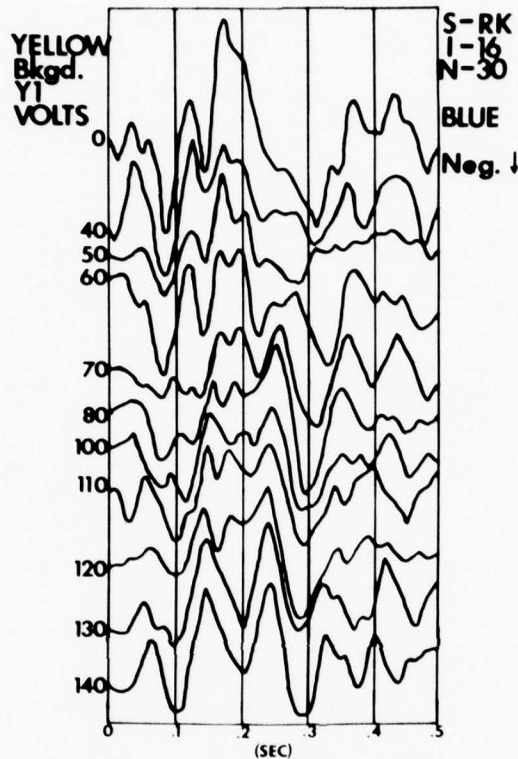


Fig. 2. Responses of a subject to blue flashes upon a yellow background. Montage: Oz to linked earlobes. This should be viewed obliquely in order to see the trends most clearly.

In Fig. 2 responses are shown for blue flashes against a yellow background for various intensities. The blue-yellow paradigm is ideal for helping to determine whether there are indeed sets of color specific components. Because of the spectral characteristics of the three basic color processes, which have been determined by well established psychophysical techniques, stimulation by the blue flash will affect primarily the blue and the green. The red processes will be affected to a slight degree, but for present purposes this can be ignored. Likewise, the yellow background will affect only the green and red processes leaving the blue relatively unaffected. It is to be noted that green would be affected by both

the stimulus flash and by the steady background light, a fact crucial for the logic of this experimental design.

It is assumed that the in-dark waveform evoked by the blue flash (top of Fig. 2) is made up of blue and green related elements. As the background is increased the amplitude of any green-related elements should diminish and can thereby be identified. An overview of Fig. 2 clearly shows what has occurred in the evoked waveform as the background was increased. The prominent positive peak at 120 msec was markedly diminished and eventually completely removed. This also is true for positive peaking at 200 msec. We therefore tentatively identified these two peaks as components of the green process.

What happened to another peak was equally dramatic. One of the major features of the in-dark blue response was the marked positivity occurring at 180 msec. When the earlier (green?) component disappeared with the increasing background level, the later peak moved forward in time about 30 msec and eventually stabilized at about 150 msec. At the higher background levels another peak emerged at about 90 msec following the first, ending at about 240 msec. We concluded that these two components are related to the blue process.

On the basis of a number of facts described in our earlier paper it was concluded that the second positive peak in the red evoked waveform (Fig. 1) represented the reaction of the green process.

We have, therefore, isolated three pairs of components which we tentatively relate to the red, green and blue color processes. The red has the shortest latency, followed by the green, and then the blue. Under light-adapted conditions and moderately high flash intensities the peak latencies are around 90-100 msec for red, 120 msec for green and 140-150 msec for blue. The latencies of the second peaks in the color pairs are 180, 200 and about 240 msec, respectively.

The temporal characteristics of these tentative color components are in precise agreement with the results of earlier psychophysical studies by Pieron and his colleagues (1952) and the more recent studies on reaction time to color stimuli (Mollon and Krauskopf, 1973). The spectral desensitization technique was earlier used by Huber (1972).

The marked latency shifts shown by the green and blue components when the background was raised might be related to other data indicating opponency between the basic color processes. Apparently a very strong red response can delay the onset of the green process

by as much as 30 msec. The same seems to be true for the green/blue relationship with the green being capable of inhibiting the onset of the blue process by that amount of time.

The above discussion of the color responses is based on our work with color normal individuals. When individuals with known color deficiencies were studied the results obtained were in general agreement with our color-normal analysis, but there were marked individual differences shown among individuals with the same color vision classification (White et al., 1977).

Some of the earliest work on color responses done in our laboratory dealt with binocular summation (Bartlett et al., 1963). We have recently finished an extensive parametric study on this topic in which a number of individuals were presented a broad range of stimulus/background conditions. The usual individuality of our subjects was found also in regard to this aspect of the VER, each showing marked differences in terms of the degree of summation shown for given conditions (White et al., 1978).

Under certain conditions the degree of summation shown by a subject could be quite impressive, definitely out of line with the results of psychophysical judgements dealing with binocular summation effects. Two examples of marked summation are shown in Fig. 3. They represent the reactions to two intensities of blue flashes presented upon a rather high intensity yellow background. This stimulus background situation was overall the best for demonstrating the highest degree of summation for most of our group of subjects.

Another finding which came out of this study was the fact that some of our subjects' responses to left and right eye stimulation were quite different. This is illustrated in Fig. 4 (a). The stimulus was a relatively low intensity green flash (12 on the Grass photostimulator) presented upon a relatively high level background. Under these conditions the subject (myself) noticed that he was having completely different color perceptions under the monocular conditions with one eye producing yellow and the other green. It can be seen from the figure that when "green" was reported the red component was missing. When both the red and green components were present in the evoked response a yellow flash was seen.

SUBCORTICAL ELEMENTS IN THE VER

In our earlier paper on color evoked potentials (White et al., 1977) evidence was presented which indicated that the color specific components around 100-150 msec were related to subcortical activity. The strongest evidence was the fact that these response components could be obtained even when there was no electrode in

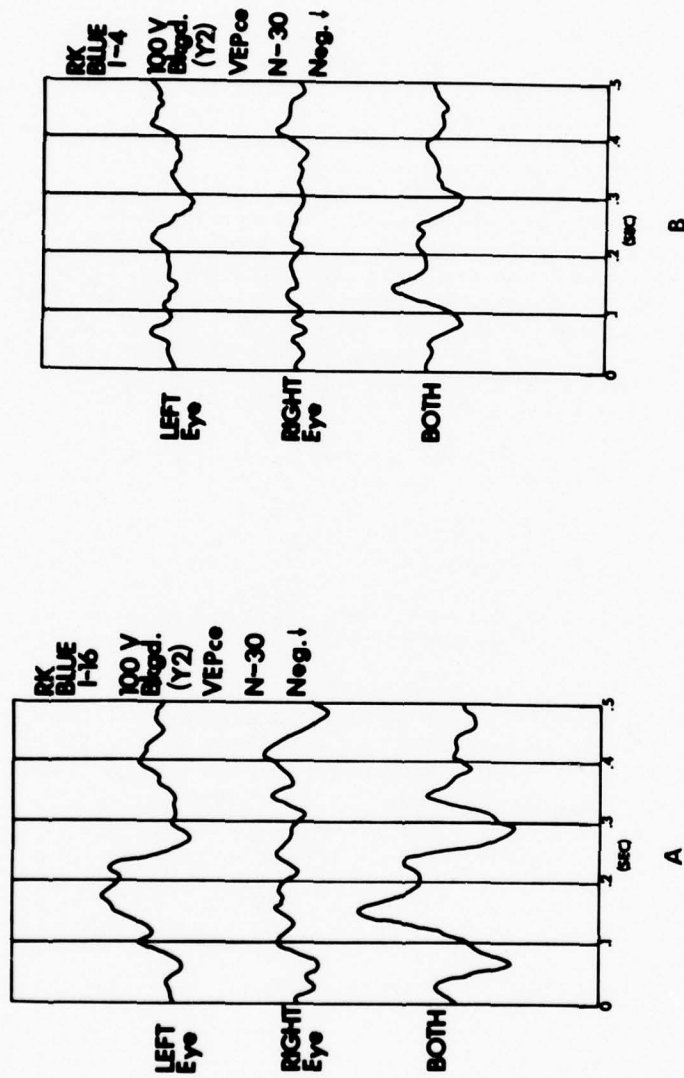


Fig. 3. Examples of binocular summation effects. Blue flashes upon a yellow background. Montage: Oz to cheekbones beneath the eye (VEP ce). (a) Flash intensity 116 (Grass photostimulator); (b) Flash intensity 14.

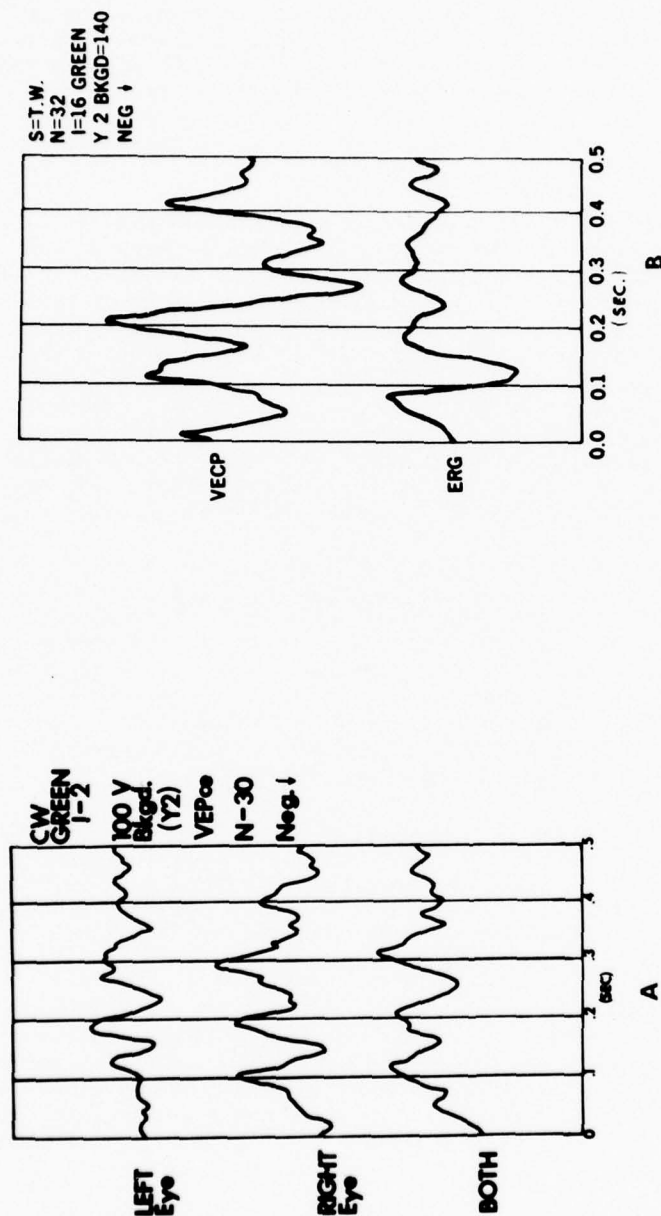


Fig. 4. (a) Example of differential monocular responses related to differences in color perception. Montage: Oz to cheekbones beneath the eyes. With right eye stimulation the subject saw a "yellow" flash; with the left a "green" flash. Note different responses around 100 msec. (b) Simultaneous recordings of VECP and "ERG". VECP montage: Oz to linked earlobes. "ERG" montage: Cheekbone beneath eye to linked mastoids. Right eye stimulated, recorded from left occluded eye.

place over the visual cortex. With the active electrode at the eye and reference electrodes at the mastoids, for example, a red flash will produce a sharp negative peak at 100 msec, precisely the time at which a sharp positive peak would be obtained with an electrode over the visual cortex with mastoids or earlobes as reference. With the eye-mastoid montage the strong component at around 200 msec does not appear, however, indicating that it is related to cortical activity.

Further evidence in this regard is presented in Fig. 4 (b), which presents the results obtained when the cortex-mastoid and eye-mastoid electrode placements were used simultaneously. It is part of a series in which the effects of various levels of background on the visual evoked potential and the electroretinogram (ERG) were being studied. As the background was raised the B-wave (rod related) disappeared, leaving only the photopic (cone) elements of the light-adapted eye. At this point it was noted that the early portions of the two waveforms were essentially mirror images of one another (from about 40-160 msec) but became completely different from that time on with the strong positive activity at 200 msec appearing only when using the cortex-mastoid montage.

The presence of the scotopic B-wave limits the usefulness of the ERG for studies such as this since only by light-adapting to fairly high levels can one get photopic responses. It has been found that responses evoked by flash stimuli can be obtained by stimulating one eye and recording from one electrode placed on the ridge of the cheekbone under the occluded eye. The B-wave does not appear on the records so obtained. The components that do appear are assumed to be related to activity at some higher level in the visual system common to both eyes.

Fig. 5 (a) presents the responses of a subject to red, green and blue flashes at two background levels. Negative is up in this figure to emphasize the similarity to the results obtained with cortex-mastoid electrode placement (but with the opposite polarity). In this case the right eye was stimulated and recording made at the left eye.

In Fig. 5 (b) we have a more extensive example of the type of responses to be obtained when the nonstimulated eye technique is used. Throughout a high intensity blue flash was the stimulus with a varying yellow background. The upper half of the figure shows the responses obtained when the right eye was stimulated and recording was made from the left eye. The reverse is true for the lower half.

The results we see here support what we said earlier; the two eyes appear to be different in their color sensitivity. In the

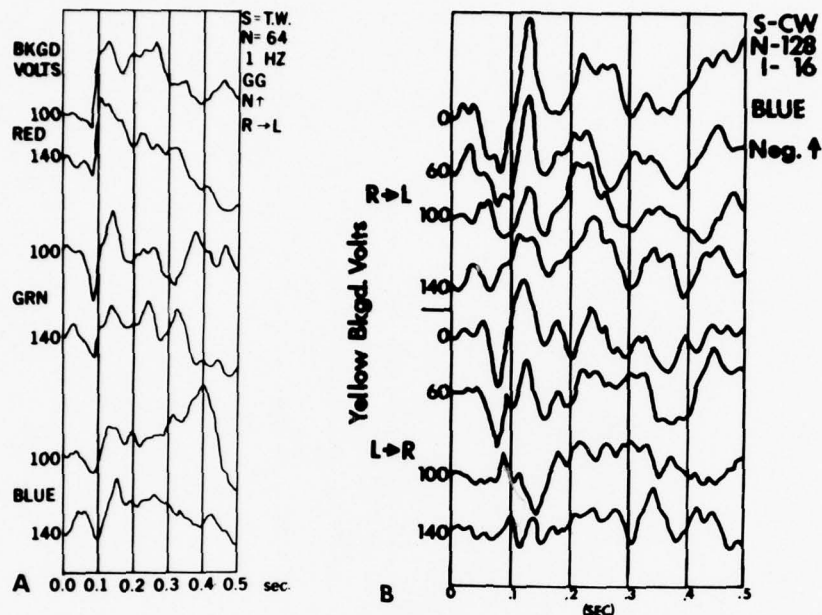


Fig. 5. (a) Responses to red, green and blue flashes upon two levels of yellow backgrounds (100 v and 150v). Montage: Cheekbone beneath eye to linked mastoids. Right eye stimulated, recorded from left occluded eye. (b) Responses to blue flashes upon yellow backgrounds. Montage: Cheekbones beneath eyes to linked mastoids. Upper records show right eye stimulated, recording from left eye; lower records show left eye stimulated and recording from right eye.

lower half of the figure (L-R) a negative peak is prominent just before 100 msec, while this is not the case in the R-L situation. This finding has been consistent for this individual. The difference is especially noticeable at the 100 volt background level.

The findings here are consistent within themselves, but are strikingly different from the records shown in Fig. 5 (a) wherein similar stimulus/background conditions were used. The very strong peaking at 150 msec which has been identified as the first blue component is not apparent as an outstanding feature.

The responses in Fig. 6 seem to provide an answer, though not now an explanation, to this problem. Here is the same subject, same flash intensity of the blue light, and with one of the yellow background levels used in Fig. 7 (100 volts). It can be seen

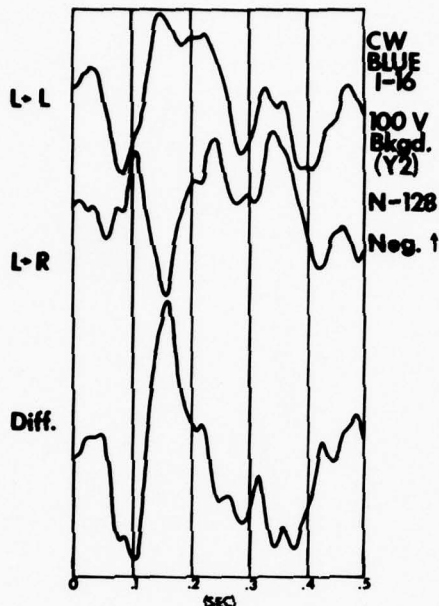


Fig. 6. Responses of subject CW to high intensity blue flashes upon a 100v yellow background. Montage: Cheekbone beneath eyes to linked mastoids. L - L: Left eye stimulated, recording from left eye. L - R: Left eye stimulated, recording from right occluded eye.

that the morphology of the waveforms are similar for the L-R condition at that background level considering the expected day-to-day variability.

The major difference to be seen in Fig. 6 is in the L-L condition, i.e., the left eye was stimulated and the recording was made from beneath that eye. In this case there is a very strong negative peak at 150 msec. The difference waveform is even more emphatic; the strong negative peak at 150 msec does not carry across to the unstimulated eye.

We would like to conclude our paper with a discussion of the evoked waveforms shown in Fig. 7. In the first part [Fig. 7 (a)] there is the comparison of the responses obtained in an eye to mastoid montage with the eye to midforehead montage. It is clear that the prominent peak at 150 msec which has been so clearly related to the "blue" component of the VEP is also dependent on the mastoid (or earlobe) electrode being used.

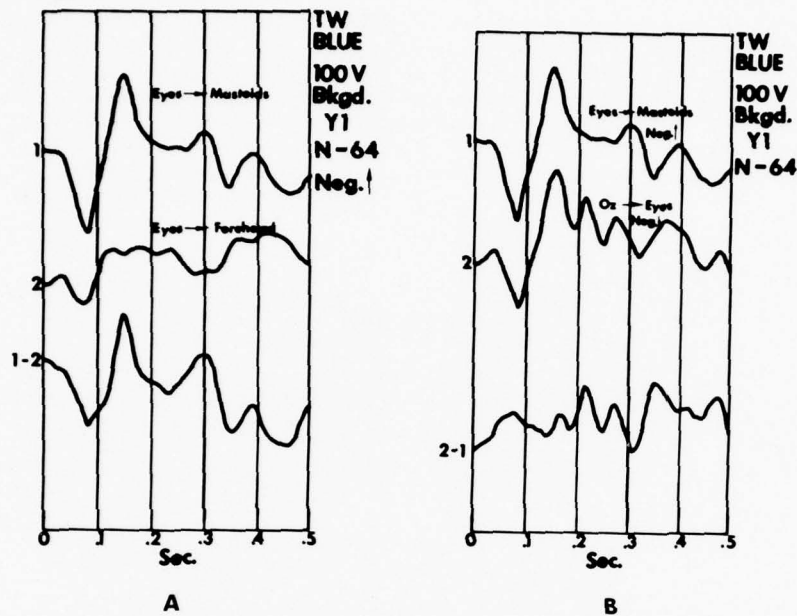


Fig. 7. (a) Responses of subject TW to blue flashes upon a 100v yellow background. Upper response: eye to mastoid; center response: eye to midforehead, a standard reference for the classic ERG; lower waveform; the difference between these two waveforms. (b) Responses of subject TW to blue flashes of 116 intensity upon a yellow background 100v. Upper waveform is eye-mastoid; middle record is cortex to eye. Lower is the difference between the other two.

The second part of Fig. 7 (b) contrasts the eye-mastoid montage with the cortex to eye montage and the cortex to mastoid montage under this particular stimulus/background situation. Again it is clear that the prominent peak at 150 msec is primarily dependent on an electrode being placed in the mastoid location while the later components require the use of a cortical electrode.

SUMMARY

Previously published findings by our group regarding color evoked potentials were replicated and examples from a recent study on binocular summation of such potentials were presented. Our

earlier suggestion that certain elements of the evoked waveform represent visual processing activity at some subcortical level was given added support by examples of evoked potentials obtained from combinations of cortical and noncortical electrode placements. The strongest evidence was that the activity between about 40-160 msec following stimulus presentation could be obtained with both the cortical and noncortical electrodes (with opposite polarities), while the activity around 200 msec and beyond was dependent on the use of a cortical electrode.

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ABSTRACTS

INTERACTIONS BETWEEN TARGET AND MASKING STIMULI:
PERCEPTUAL AND EVENT RELATED POTENTIAL EFFECTS

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The purpose of this investigation was to determine the effects of target-mask contour interactions (backward masking paradigm) on perception and visual event related potentials (ERPs). Three experiments were conducted. In the first, masking stimuli closely bordered the target on 25%, 50%, 75% or 100% of its perimeter. Increased amounts of target-mask contour interaction resulted in progressively greater decreases in ERP amplitude (Oz recordings) to target stimuli. (In all experiments a positive ERP component which appeared at 200 msec after target presentations was used in data analyses.) Perceptual masking occurred with contour interactions of 50% and over.

A second experiment examined visual ERPs to the masking stimulus alone, target alone and to a target-mask condition which produced perceptual masking. The ERPs were recorded from Oz to Cz. Perceptual masking was accompanied by significant ERP attenuation at Oz only. The Cz response was similar under all conditions. Amplitude of response at Oz was significantly greater for the mask alone compared to the target alone condition.

A third experiment compared the target-mask condition at an effective interstimulus interval for masking (40 msec) with ISIs in which target and mask were perceived either as simultaneous (10 msec) or successive (100 msec) presentations. The most interesting finding was that target-mask conditions which did not produce masking (10 msec and 100 msec ISIs) were not accompanied by ERP amplitude attenuation. The effective masking condition (40 msec ISI) resulted in significantly attenuated ERP amplitudes. The ERP changes were specific to Oz recordings since Cz records showed no amplitude changes for the different conditions. The mask alone condition again produced a significantly larger response than target alone. This difference may have been due to the larger amount of perceived contour for the mask alone (sixteen sides) vs. target alone (four sides). The results suggest that cortical excitatory-inhibitory activity produced by target and mask stimuli is reflected in ERP recordings obtained from over the occipital cortex, but not at the vertex.

CEREBRAL ORGANIZATION OF EVENT RELATED POTENTIALS
ANALYZED BY MULTIDIMENSIONAL SCALING TECHNIQUES

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One of the most important but difficult problems in the analysis of event related potentials (ERPs) is the determination of interareal relationships from simultaneously obtained averaged recordings. One approach to this problem is suggested by the recent configurational analysis of the spontaneous EEG using multidimensional scaling reported by Beatty (Beatty, Neuroscience Letters, 8 (1978) 99-104). The present paper reports the results of a similar analysis of interareal relations for visual, auditory and somatosensory ERPs using data originally described by Goff and Allison. From these data the latencies of ten reliably appearing early or middle (less than 150 msec) components at eighteen sites, were used to compute a half-matrix of the Euclidean distances between all possible electrode pairs for each stimulus type. The three resulting matrices represent the measured functional distances between electrodes for which a two-dimensional configurational solution was attempted using INDSCAL, a three-way multidimensional scaling program.

INDSCAL was able to achieve a low error two-dimensional solution with the following properties. First, the obtained dimensions might naturally be labelled anterior-posterior and left-right. Second, the grouping of recording sites in this functional space indicates a clear division between frontal and posterior cortex along the anterior-posterior dimension. Third, the individual solutions for the three stimulus types indicate the anterior-posterior dimension dominates the configuration for the visual ERP, whereas the left-right dimension predominates for the somatosensory ERP. Finally, for all ERPs the orderly representation of occipital, parietal, central and frontal zones, flanked on each side by temporal cortex, may be reliably discerned. Thus, it appears that the configurational maps produced by multidimensional scaling provide a means of representing functional units of the human cerebral cortex in a comprehensible and meaningful fashion.

ELECTROPHYSIOLOGICAL INDICATORS OF COGNITIVE DEFICITS
IN CHRONIC ALCOHOLICS AND GERIATRIC SUBJECTS

H. Begleiter and B. Porjesz

Chronic alcohol abuse is known to produce information processing deficits. It has been postulated that these cognitive deficits are quite similar in alcoholic patients and in geriatric subjects. Therefore, we conducted a visual evoked potential (VEP) experiment designed to assess information processing deficits in chronic alcoholics, as compared to geriatrics and matched controls, using a P3 paradigm.

The experimental design required that the subject respond to rarely occurring (8.3%) target stimuli only, while withholding responses to frequently occurring (83.3%) non-target stimuli and rare (8.3%) "novel" stimuli. The target shape and non-target shape were alternated over four blocks (96 stimuli/block) in the first condition (Long Blocks) and were alternated four times as often (16 blocks) in the second condition (Short Blocks) containing 24 stimuli/block. Monopolar VEPs were recorded at Oz, Fz, Cz, Fz, F3 and F4, and peak-to-peak measurements (P1, N1, P2, N2, P3), as well as principal component factor analyses with varimax rotation, were performed on the data. This paper is limited to a discussion of the Fz electrode.

Our results indicate that the alcoholics manifested significantly depressed or absent P3s to target stimuli when compared to both the normal controls and the geriatric subjects. On the other hand, the geriatric subjects displayed significantly delayed latencies when compared to both the alcohol and control groups for all conditions. Therefore, our data does not support the view that CNS deficits in alcoholics are similar to those in geriatric subjects.

GSR, AEP AND CNV IN DEPRESSED PATIENTS AND HEALTHY CONTROLS

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In eighteen patients with primary affective disorders and twenty-seven healthy, age matched controls, GSR (skin resistance level, number of spontaneous fluctuations, amplitude and habituation rate of orienting response, AEP and CNV (Fz, Cz) were measured in response to auditory stimuli. During the non-response condition, the resting subject heard pairs of tones (ISI 2 sec, III 7-12 sec), while in the response condition, he had to react upon the second stimulus by pressing a key.

Depressed patients develop AEP amplitudes (N1-P2 differences) which average 15% smaller and CNVs which are about 50% smaller than those of healthy controls.

		Patients	Controls	
AEP (N1-P2 μ V)	Fz	24.1 \pm 9.6	31.3 \pm 9.5	p<0.01
	Cz	22.8 \pm 10.4	31.7 \pm 16.2	p<0.05
CNV (μ Vsec)	Fz	7.3 \pm 6.6	17.4 \pm 9.3	p<0.001
	Cz	10.4 \pm 7.7	19.2 \pm 10.5	p<0.001

The last finding is at variance with the results of Small and Small (1971), in as far as these authors found smaller CNVs only when warning stimulus and imperative stimulus differed in modality and not when a single modality was used. A higher degree of inhibition in depressed patients, as measured in GSR, is confirmed in respect to number and mean amplitude of GSR orienting responses during response condition: depressed patients show less response and smaller response amplitudes. Our hypothesis that inhibition as measured in GSR is positively correlated with a reduction of AEP is only partially supported by the data: mean AEP amplitude is positively correlated with the number of spontaneous fluctuations and is negatively correlated with skin resistance level - but in the depressed group only. On the other hand, CNV (Fz) is negatively correlated with the number of spontaneous fluctuations and positively with skin resistance level - also in the depressed group only. Finally, mean GSR amplitudes during the response condition are positively correlated with CNV (Fz) in patients, as well as in healthy controls.

SCALP-RECORDED VISUAL EVOKED SUBCORTICAL POTENTIALS IN MAN

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Short latency auditory and somatosensory subcortical evoked potentials (EP) have been recorded from the human scalp. Similar visual evoked potentials have not been described in man. In animals, however, short latency EP have been recorded from the optic nerve, tract, lateral geniculate body, optic radiation and visual cortex. We describe similar scalp-recorded visual EP in man.

EP to bright light flash stimulation were recorded from the scalp of fifteen adults. This response consisted of a series of potentials which were distributed widely over the scalp. The onset latency of the response recorded over anterior frontal regions was 9-17 msec, and the peak latency of the first potential was 11-21 msec. The oscillations (100-160 cps) persisted for up to 90 msec. The onset latency of the response recorded over central-parietal-occipital regions was 13-24 msec, and the peak latency of the first potential was 15-27 msec. These oscillations (80-180 cps) persisted for over 100 msec in some subjects.

These EPs were greater in amplitude at midline and parasagittal recording locations than in temporal leads. Over posterior head regions the first few waves were similar in amplitude in central, parietal and occipital leads and were lower in amplitude than subsequent ones. In some subjects the subsequent oscillations were similar in amplitude at central, parietal and occipital sites, while in others they were more prominent in occipital leads.

The source of these potentials recorded over anterior frontal regions is uncertain. Similar potentials have been recorded from the optic nerve and tract of animals and from the ERG of animals and man. However, under the conditions of sustained light adaptation used in this study, the optic nerve and tract potentials recorded in animals are maximal, but the ERG potentials are attenuated and are not consistently recorded in different preparations. This suggests that the oscillatory potentials recorded from anterior scalp regions in man may arise, at least in part, in anterior optic pathways including the optic nerve and tract.

The distribution of the oscillations recorded from posterior scalp regions is not consistent with an origin in the ERG. Their short onset latency and frequency are similar to the oscillatory potentials recorded from the lateral geniculate body, optic radiation and cortex of animals. It seems likely that these potentials arise in these structures.

EFFICACY OF THE SCALP-RECORDED VISUALLY EVOKED POTENTIAL
IN DEMONSTRATING MISROUTING OF OPTIC PROJECTIONS IN MAN

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Visual systems of albino mammals, including humans, are anomalous. Anomalies include: (1) reduced uncrossed optic projections, (2) disorganized lamination of lateral geniculate nuclei and (3) disorganization of projections to visual cortex. Abnormalities have been verified in nine species of mammals, including humans. Experiments with animals and humans have shown that visually evoked potentials (VEPs) recorded from surface electrodes reflect the disorganized retinogeniculostriate projections. The organization of uncrossed and crossed optic projections may be examined by comparing effects of binocular versus monocular stimulation while recording VEPs from both hemispheres.

Binocular versus monocular stimulation produces no significant alteration of the VEP in most normally pigmented humans. VEPs were recorded from sixty human total albinos and from ten human ocular albinos. Approximately 70 percent of human albinos and ocular albinos show significant alteration of VEPs following monocular stimulation, with one or more components of the VEP missing or significantly attenuated. Efficacy varies between luminance onset-offset, pattern onset-offset and pattern-reversal stimuli.

The asymmetric VEPs of monocularly illuminated human albinos reflect the disorganization of optic fibers similar to that reported for other albino mammals. The asymmetrical VEPs of human albinos are probably due to disorganization of cortical projections similar to the disorganization detailed for the Siamese cat. The missing VEP components are most likely the result of disorganized geniculostriate projections generating potentials in abnormally oriented areas of the visual cortex. The effect of misrouting of optic afferents found in albinos is similar to shifting the visual field midline (0° meridian) up to 20° . In the albino this shift is analogous to the effect of partial field stimulation in a normally pigmented subject. Changes in components of the VEP of monocularly stimulated human albinos are similar to those in the VEP of patients with homonymous hemianopsia or localized unilateral macular scotoma affecting the first 20° of the horizontal field. Scalp-recorded VEPs detect the abnormal cortical projections in patients with various types of albinism reflecting their lack of a normal neuronal substrate for cortical binocularity of vision.

EVENT RELATED BRAIN POTENTIALS IN RESPONSE TO CONSCIOUS AND
NON-CONSCIOUS STIMULI: HEMISPHERIC SPECIALIZATION
AND THE EFFECTS OF ATTENTION

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Two experiments were performed on evoked brain potentials in response to consciously detected and non-conscious stimuli. The purpose of Experiment I was to determine whether selective attention influenced EPs to subthreshold stimuli. In the first experiment ten subjects were exposed to alternating stimuli in four classes: above threshold auditory (aa) and visual (av), below threshold auditory (ba) and visual (bv). Incremental thresholds were obtained for visual and auditory stimuli. Subjects received the following conditions: Attend Auditory (AA); Attend Visual (AV). EEG was recorded from O2, T4 and F4. The main hypothesis tested in the present data is that the amplitude of the EP in response to unconscious stimuli will be enhanced during attention to the modality of the target stimulus. The results confirmed the prediction for visual stimuli; in the seven subjects showing an EP in response to bv stimuli, N1 at F4 was significantly higher during AV versus AA. Although we recorded from only right hemisphere leads in Experiment I, in pilot work the T3 EP to suprathreshold stimuli was larger than the T4 EP, with the opposite obtained in response to subthreshold stimuli. Experiment II was designed to: a) further explore this finding; b) develop more rigorous psychophysical methods for characterizing conscious and unconscious stimuli. Six right-handed subjects were exposed to a two-interval forced choice detection paradigm. Two standard tones separated by a 1 sec interval were presented binaurally. Subjects were required to detect in which interval a 40 msec amplitude increment occurred. The amplitude of the increment was varied to maintain 75% correct detection. Subjects also rated their degree of confidence in their response. EEG was recorded from T3, T4, F3 and F4. For each subject, EPs were obtained in response to correctly detected stimuli and misses with the constraint that the mean amplitude increment be equivalent for both sets. The results revealed significant differences in the N2-P3 component between hits versus misses for T3 and F3 but not for T4 and F4. The T3 response to hits was larger than that for T4; in addition, the difference between hits versus misses was greater in T3 versus T4. Five of six subjects showed a difference of greater than 2 μ V between hits versus misses in T3 with only one of six showing a comparable difference in T4 ($p=.039$). These findings suggest that identical stimuli, which are detected versus missed, evoked different brain responses and specifically indicate that the left hemisphere shows an enhanced responsiveness to conscious stimuli compared to the right.

CLINICAL USE OF THE ABR IN AN INFANT INTENSIVE CARE UNIT

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The auditory brain stem response (ABR) yields information on both the neurological and the audiological status of infants, children and adults. We have developed a procedure for extracting each type of information for separate study and have applied it to over 100 premature infants (28 to 42 weeks gestational age) in an intensive care unit. The procedure is based on these well known facts: (1) the interval between waves I and V is constant at a given age; (2) the threshold lies close to that stimulus intensity where wave V is smallest in amplitude and longest in latency.

Using click stimuli at rates of 37 or 70 per second, we have identified four infants with neurological disorder, eleven with audiological disorder and two with both. The I-V interval and the response threshold were considered to be normal in 91. For the audiological cases, the clinical history was analyzed in an effort to identify the risk factors for hearing loss and estimate their importance.

Nine such factors were identified, and the combination of perinatal hypoxia and postnatal acidosis appeared most frequently.

THE EVOKED POTENTIAL AS A MEASURE OF BRAIN DYSFUNCTION:
AGING, DOWN'S SYNDROME, ALCOHOLISM, AMYOTROPHIC
LATERAL SCLEROSIS AND RENAL DISEASE

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In an attempt to develop the evoked potential (EP) technique into a useful procedure for evaluating brain dysfunction, we have recorded EPs from several hundred normal subjects whose ages ranged from the first through the eighth decade. These data reveal striking age related changes which must be taken into account when evaluating patient populations.

EPs recorded from 66 Down's syndrome (DS) individuals aged 5-62 years were significantly larger than those of normals. While the EPs of normals clearly habituated over time, those of the DS group did not. The EPs of the DS group did not show age related trends similar to those observed in the EPs of normal subjects. These findings support the concept that deficits in central inhibition characterize the DS brain.

To determine if alcoholism promotes CNS aging, twenty young alcoholics, young normals and normal oldsters were compared with respect to EPs, WAIS subtests and a battery of neuropsychological tests. Despite a nearly forty year age difference between the young alcoholics and the oldsters, the EPs and test performances of the two groups exhibited a surprising number of similarities.

Amyotrophic lateral sclerosis (ALS) is a chronic, progressive degenerative disease which selectively destroys the motor system from cortex to anterior horn cells. Somatosensory EP waves of ALS patients were delayed and of smaller amplitude than those of normals. We speculate that these changes in somatosensory EP waves reflect alterations of motor or pyramidal feedback acting on the somatosensory system.

The short term effects of hemodialysis on the CNS were assessed with EP and neuropsychological test measures which were obtained 1, 24, 42 and 66 hours following dialysis. A highly consistent relationship between time since dialysis and EP latency was found. Latencies were shortest at 24 hours following dialysis and longest at 66 hours. Performance on two tests of visual-motor speed and accuracy paralleled the EP latency findings: performance was best 24 hours following dialysis. The results indicate that there are consistent changes in the CNS as time since dialysis lengthens.

A NEW TEST OF BRAIN FUNCTION:
BRAIN STEM TRANSMISSION TIME (BTT)

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For several years auditory nerve and brain stem responses (BSR) have been used routinely in auditory diagnosis to give objective information regarding both hearing threshold and site of lesion. Recently the value of BSR in neurological diagnosis, lesion localization and psychopathology has been demonstrated. One of the characteristic electrophysiologic response deviations observed is prolonged response latency of later waves which is best quantified by measuring the time interval between the latency of the first response wave (N) and a certain late brain stem response wave. This measure has been called brain stem transmission time (BTT). The purpose of this study was to describe BTT as a recorder in normal subjects under various conditions. BTT was recorded in normal subjects in several age groups from neonates to late childhood-adulthood and under several stimulus conditions.

BTT is the time interval between the peak of compound auditory nerve response (wave 1) (the input to the brain stem) and the trough of the earlobe positive wave generated in the region of the inferior colliculus (output) BTT is longest in neonates and approaches adult values at the age of three years. BTT is relatively independent of click intensity, conductive (middle ear lesion) hearing loss, click rate (except for high click rates) and click frequency (filtered clicks).

This finding that for a given age group, BTT is generally independent of most stimulus conditions, makes it a useful, functional test of brain stem activity in audiology, neurology and psychopathology.

EQUIVOCATION IN PREDICTION VERSUS NO-PREDICTION SCHEDULES:
EFFECTS ON ERSF MEASURES

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The classical CNV paradigm involves a static S1-S2 relationship which is an inadequate analog of real-life learning situations in which anticipations and expectancies are developed. The P300 component may more plausibly be associated with imperative events and antecedent psychological factors.

Six experiments were performed in a series on the same subjects (N=14 adults, half strongly dextral, half strongly sinistral). Three paradigms were employed: 1) prediction-response to accuracy of prediction; 2) prediction-response to accuracy of stimulus sequence; 3) no prediction-response to accuracy of stimulus sequence. Four experiments involved analysis or synthesis of simple geometrical figures; the other two involved presentation of alphabetic series. The differential motor response of the subject followed S3.

Preliminary ANOVA results (for sites iP4, iP3 only) indicate that S2-S3 negativity (CNV) varies greatly between schedules. For certain conditions in interaction there are significant handedness groups differences, and these groups also differ in interhemispheric response.

The difference between hemispheres in post-S1 positivity (P300) (right hemisphere amplitude greater than left) is higher when the sequence of stimulation is incorrect than when it is correct. Post-S3 positivity (P300) is significantly small in the alphabetic schedule compared with the other paradigms. Overall, the amplitudes of this component for correct versus incorrect outcome sequences, interact with the nature of the schedule.

These preliminary results show that the magnitude of ERSF components is much affected by stimulus-organism-response factors, singly and in interaction, which are omitted from many experimental designs.

THE UTILITY OF ERPs IN DETERMINING AGE-RELATED DIFFERENCES

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ERPs provide unique information about age related neural and cognitive deficits. ERPs are better than behavioral techniques alone because they can: (1) be recorded to both unattended and attended stimuli; (2) be recorded from subjects performing no task; (3) supplement reaction time (RT) measures for estimating timing of different mental events. We describe three experiments in which ERPs were used in these ways to compare young (20-29 years) to old (74-89 years), non-senile, extraordinarily healthy women.

To determine if elderly subjects can ignore irrelevant auditory stimuli and detect target stimuli, we used a technique devised by Hillyard et al. (1973). The results for N1 reflected that both groups could attenuate irrelevant stimuli, while the results for P3 indicated that, although elderly subjects could identify targets, they were slower than were young subjects.

To demonstrate age related neural differences without demanding task involvement we recorded ERPs to four tone intensities from passive subjects. The amplitude of N1 increased with intensity for young and old subjects. The amplitude of P2 increased with intensity for young but decreased for old subjects. The amplitudes of an early peak (P1) and a late sustained potential were more negative in young than in old subjects.

To estimate separately the speed of some mental processes, we used both RT and the latency of P3 to the target in a Sternberg task. On each trial, subjects received a memory set of 1-4 digits followed by a target digit. Subjects pressed one of two buttons indicating whether the target was a member of the memory set. RT P3 latency to the target were increasing linear functions of the number of items in the set. Some of the slopes and intercepts of these functions, the mental processes they may reflect and the time taken to complete the processes for old and young are listed in the table below.

	RT Intercept	P3 Latency Slope	P3 Latency Intercept	RT-P3 Latency Intercept
Hypothetical mental processes	Encoding + Motor	Memory Scanning	Encoding	Motor
Time to complete the process:				
Old	1028 ms	27 msec/digit	448 msec	582 msec
Young	720 ms	29 msec/digit	369 msec	350 msec

APPLICATION OF ERPs IN THE STUDY OF DRUG USE AND ABUSE IN MAN:
A CLOSE LOOK WITH MORE SENSITIVE TASKS
AND MEASUREMENT TECHNIQUES

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Components of the sensory evoked response later than 75 msec are limited to processes other than pure sensory stimulus reception. Although there is some disagreement as to the exact nature of this process(es), as well as which component(s) appears to reflect which process(es), there is no doubt that these latter components involve an evaluation of the stimulus at some level, and can be dependably altered by slight psychological manipulations. The components in 75 to 250 msec range are also altered by a variety of psychoactive drugs. Most often these midrange components are decreased by depressants and increased by stimulants. However, the effects of few drugs have been studied on components later than 250 msec in paradigms designed to maximize these components.

Drugs are often abused for their psychoactive properties. Are these altered perceptual states detectable and quantifiable by ERP methods on other than the sedation continuum? Do abused drugs have some common effect on the ERP? To answer these questions, we have studied the effects of single doses of alcohol, hexobarbital, THC (marijuana), nicotine and morphine on the auditory ERPs of normal, healthy adults performing the oddball task. For all drugs except alcohol, the ERPs were recorded at times of maximal drug effects. All drugs produced a decrease in P300 of the auditory response to the rare tone. Table 1 lists the percentage decrease from pre or control for each of the drugs. These and possibly other psychoactive drugs alter or reduce the cortical processing of rare occurring stimuli.

Table 1

Drug	Dose	Test Time After Dose	% Decrease at P _z
Ethanol	1 ml/kg Oral	2.5 hr	9%
Morphine	.14 mg/kg I.M.	45 min	18%
Hexobarbital	500 mg Oral	3 hr	20%
Nicotine	One "Camel"	At end of smoking	27%
THC	10 mg THC Smoked	15 min	30%

AUDITORY EVOKED POTENTIALS AND PSYCHOPHYSICAL PARAMETERS
IN CIRCADIAN STUDIES

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In the past few years there has been increasing evidence of a close relationship between detection behavior and the averaged evoked potential (AEP) and the importance of nonsensory, as well as sensory, factors has also been established (Hirsh, S.K., Psychon. Sci., 1971, 22, 173-175). The relationship between these nonsensory factors and the P3 component has been studied chiefly within the context of the Theory of Signal Detectability (Hillyard, S.A. et al., Science, 1971, 172, 1357-1360). With respect to circadian variation in auditory psychophysical performance and related AEPs, the results are not unequivocal (Conroy, R.T.W.L. and Mills, J.M., Human Circadian Rhythms. J. and A. Churchill: London, 1970). The main objective of the present study is to clarify this problem.

In three diurnal studies (10.00 and 19.30 h) we employed yes/no ratings and 2AFC procedures. The subject had to judge whether or not a burst of white noise contained a weak sinusoidal signal. No evidence was found for diurnal fluctuations of perceptual sensitivity, response bias, P3 amplitude or the relationships between the two detection parameters and P3. We also conducted an around-the-clock experiment involving a rating task at four different times of the day (04.00, 10.00, 16.00 and 20.00 h). The AEPs were analyzed by principal components analysis. For some components slight but significant effects were found. In current data analysis, particular attention is given to the relationship between single EPs and detection behavior by the use of multivariate analysis procedures; latency characteristics of the single EPs as well as alternative detection parameters, are under investigation. Our present approach is directed at characterization of detection and performance in terms of perceptual sensitivity and response bias on the basis of single EPs. This should enable us to establish short-term changes in neurophysiological correlates of detection behavior.

EFFECTS OF METHYLPHENIDATE ON HYPERACTIVE CHILDREN'S
EVOKED RESPONSES DURING PASSIVE AND ACTIVE ATTENTION

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This study was aimed at assessing the effects of methylphenidate on hyperactives' evoked responses (ERP) and performance in the Continuous Performance Test (CPT). Eighteen hyperactive boys were removed from methylphenidate treatment for 6-51 days and were tested in two different sessions in which they received methylphenidate (0.3 mg/kg) and placebo in multiple blind fashion and counter-balanced order. In addition, seventeen normal boys were tested without drugs. For both samples vertex-derived evoked potentials were recorded to the fifty go- and the fifty preceding no-go stimuli of the CPT. When the task was administered without a requirement to respond, there were no electrophysiologic differences between hyperactive and normal children.

In the active CPT, normal children made fewer errors of omission ($F(1/31)=18.06$, $p < .001$) and commission ($F(1/31)=21.27$, $p < .001$) and displayed faster reaction times ($F(1/31)=6.33$, $p < .025$) than hyperactives tested under placebo. In addition, the late positive component (LPC; P320) of the evoked responses evoked by both go- and no-go stimuli was smaller in placebo treated hyperactives than in normals ($F(1/31)=5.47$, $p < .05$). Methylphenidate increased the amplitude of hyperactives' LPC ($F(1/13)=4.88$, $p < .05$) and ameliorated their performance, especially commission errors ($F(1/13)=5.55$, $p < .05$) and reaction times ($F(1/13)=4.69$, $p < .05$). These results confirmed previous findings of normalization by methylphenidate of hyperactives' performance and electrophysiologic activity during active attention.

EVOKED POTENTIALS IN SENILE DEMENTIA

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In order to evaluate the modifications of brain evoked responses in senile dementia we performed two studies.

In the first one, visual evoked responses (VER) to flashes were recorded at occipital (Oz) and vertex (Cz) leads in twelve patients suffering from severe senile dementia and twelve young normal adults. Whereas the occipital responses were rather similar in the two groups, vertex responses were of lower amplitude in patients than in controls and sometimes were hardly discernible. Therefore, the vertex responses to flashes seemed to be impaired in senile dementia.

In order to further elucidate this finding and to obtain a control group matched for age, we performed a second study on ten patients suffering from simple senile dementia (SD; mean age = 83.4 years), seven patients suffering from Alzheimer's disease or senile dementia evolving towards an Alzheimer condition (AD; mean age = 73.5 years). The experimental procedure was similar to that used in the precedent study; in addition, we investigated the responses to auditory stimuli (AER). The analysis of the results revealed that in SD, the vertex VERs presented a quite standard configuration, but with longer latencies and greater interindividual variability than in controls. In AD the vertex VERs were not discernible, the N1-P2 component being replaced, on the grand mean (obtained by averaging all responses of all patients), by a positive wave of low amplitude. On the other hand, the vertex AERs were present in all subjects, the latencies being longer in patients than in controls. Therefore, in AD the vertex VER is missing, while the vertex AER is preserved. Apart from its clinical implications, this finding puts into question the generally admitted opinion of the nonspecificity of the vertex response.

ELECTROPHYSIOLOGICAL AND BIOCHEMICAL STUDIES
IN AUTISTIC CHILDREN TREATED WITH VITAMIN B6

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Previous studies have indicated that certain autistic children are favorably influenced by vitamin B6 (Rimland B., Callaway, E. and Dreyfus P., *Am. J. Psychiat.*, 1978, 135, 472-475). Our recent laboratory study of forty-four autistic children disclosed fifteen who were improved by large doses of B6. In addition, many of these children showed a large decrease in the excretion of urinary homovanillic acid during the B6 treatment.

A study of event related potentials (ERP) in some of these children has been carried out before and during the treatment with B6. Thirteen autistic children (average age, 9.5 years) and eleven normal children (10 years) were recorded. Following a classical conditioning paradigm, sound (1 KHz, 25 dB, 4 msec) was used as the conditional stimulus and light (1 200 Lux, 0.1 msec) as the unconditional stimulus. Interstimulus interval was 800 msec. Evoked potentials (EP) were recorded from the vertex and from the occiput and measured in three windows: 0-100 msec (early EP), 100-400 msec (medium EP), 400-800 msec (late EP).

Before treatment, early EP were larger ($p < .05$), and medium EP smaller ($p < .001$), at the vertex in autistic children. Late negative EP percentage was higher ($p < .05$) in normal children. B6 treatment reduced early EP ($p < .02$), enhanced medium EP ($p < .01$) and increased negative EP percentage ($p < .05$) in autistic children. The reduction in homovanillic acid excretion was observed only in the autistic children and not in the normal children. Thus, a tendency to normalization of electrophysiological as well as biochemical data was observed in autistic children under vitamin B6 treatment.

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VISUAL EVENT RELATED POTENTIALS OF PILOTS AND NAVIGATORS

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Recent research suggests relationships between hemisphere lateral asymmetry, habituation and occupational performance. This center is evaluating these hypotheses on several Navy occupational groups. The present study is based on analyses of VERP data and information processing task performance of a group of 58 aviators from a Navy fighter squadron (28 pilots, 30 navigators). Eight channels of VERP data (F3, F4, C3, C4, P3, P4, O1, O2) were acquired by a NOVA 2 computer acquisition system installed in a mobile laboratory parked inside the squadron hangar. Technical problems encountered in this operational environment will be discussed. A simple recognition information processing task was performed by each subject prior to VERP acquisition. The pilot group consisted of thirteen instructors and fifteen students. Amplitude variates (μV_{rms}) at C3 ($F=6.53$, $df=1,56$, $p<.02$) and F3 ($F=5.28$, $df=1,55$, $p<.05$) discriminated pilots from navigators. Seventy-one percent of aviators were correctly classified ($X^2=8.35$, $p<.01$). C3 amplitude was less than C4 within the navigator group ($t=3.10$, $df=58$, $p<.01$), but not within the pilot group. Total hemisphere asymmetry ($F=5.94$, $df=1,56$, $p<.018$), site ($F=186.88$, $df=3,168$, $p<.001$) and hemisphere asymmetry-by-site interaction ($F=3.41$, $df=3,168$, $p<.019$) were significant for all subjects. VERP habituation was assessed by comparing VERPs of the first fifty flashes with the second fifty flashes. Habituation was statistically significant ($F=5.98$, $df=1,27$, $p<.021$) for instructors, but not students. No reaction time differences in information processing were found between the groups. The pilots and navigators were placed in a high or low group based on performance ratings; P4 was greater than P3 amplitude for the high group pilots, P3 was greater than P4 amplitude for the lows. P3 was greater than P4 amplitude for the high group navigators, while P4 was greater than P3 amplitude for the lows. Asymmetry (R-L) standard deviations (SDs) were greater for both low pilot and navigator groups than for the high groups. The SDs were greater in the parietal-occipital areas than in frontal-central areas for the low groups. Other Navy groups have shown similar VERP-performance relationships, low performers having greater VERP SDs than high performers (e.g. trainees on a sonar simulator).

EFFECTS OF SLOW CORTICAL POTENTIALS ON REACTION TIME
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The relationship between slow cortical potentials (SCP) and response latency was investigated by inducing different shifts of SCP: visual feedback of SCP was provided by means of a little sketched rocket moving across a television screen into one of two goals during intervals of six seconds each; subjects were asked to direct the rocket into one of the goals depending on one of two signal tones which were presented in randomized order.

In the present experiment consisting of two identical sessions, series of reaction time trials alternated with series of feedback trials; during reaction time trials subjects heard the same signal tones as during the feedback trials and were additionally asked to escape an aversive noise following the signal tones by pressing a microswitch with their dominant (right) hand. Two groups of ten subjects each were investigated, one group receiving feedback of C4-recording of SCP, the other group receiving a C3-feedback.

Results demonstrate that subjects achieve significant instrumental control of SCP. During feedback intervals negative shifts were more pronounced in the right hemisphere (C4) than in the left (C3). The better control of SCP was achieved under conditions of C4-feedback. This result can be explained by the hypothesis that our feedback - spatial representation - was processed in the right hemisphere. In reaction time trials both groups showed pronounced differences in SCP between required negativity and required positivity. After feedback training, response latency was significantly shorter in trials with required negativity. An analysis of covariance for response latency with C3- or C4-scores respectively as covariate provided significant regression constants in both groups only for C4 (right hemisphere). This does not support a motor hypothesis which would suggest that differences in SCP recorded from sensorimotor areas (interpreted as motor potentials) are responsible for differences in response speed. Interpreting SCP as sign of (readiness for) information processing would also suggest that differences in response speed - as observed in the present reaction time task - may be due to differences in SCP but not necessarily due to differences recorded from the primary motor areas of the right hand.

EFFECT OF SOUND PRESSURE DIRECTION AND FREQUENCY
SPECTRUM OF CLICKS ON BRAIN STEM RESPONSES IN CHILDREN

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Both immaturity and high frequency hearing loss increase differences in brain stem responses to rarefaction and condensation clicks. Recent reports suggest abnormal brain stem responses to combined rarefaction and condensation clicks in autistic and other developmentally disabled children. Because of these developments, a parametric study of the influence of both the direction of sound pressure and the frequency spectrum of click evoked acoustic stimuli on brain stem responses in children seem advisable. Brain stem responses to four types of acoustic stimuli were collected from nine normal and six autistic children. The stimuli were either rarefaction or condensation clicks with peak acoustic energies of either 3150 Hz or 5000 Hz. All clicks were monaurally delivered at a rate of 10/sec at 68 dB (HL). Responses were recorded from a vertex to ipsilateral mastoid derivation. The peak latencies of vertex positive waves I, II, III, IV and V and brain stem transmission time were measured in response to each of the four types of clicks separately. Significant interactions between the influence of the direction of sound pressure and the peak acoustic energy of the stimulus occurred. Rarefaction (R) clicks induced a significantly earlier wave IV response than did condensation (C) clicks, regardless of peak acoustic energy, while wave I and wave II latencies were significantly earlier in response to R than to C clicks only at the higher peak acoustic energy. The C-R difference was significantly greater in response to the 5000 Hz than to the 3150 Hz clicks for wave II. Five thousand Hz clicks induced a significantly later wave II response than did 3150 Hz clicks for C clicks and a significantly earlier wave II response for R clicks. There were no such differences in respect to the other peaks when responses to C and R clicks were computed separately. On the other hand, when the responses to C and R clicks were algebraically combined in the computer (as is common practice), these differences were not seen while the latency of wave IV was significantly later in response to 5000 Hz clicks than to 3150 Hz clicks. The latter finding was not reflected in differences associated with separate computations of responses to R and C clicks. These results suggest that the practice of combining brain stem responses to R and C clicks may be misleading in some applications and that it is necessary to know the acoustic characteristics (frequency spectrum) of the click stimulus. On the other hand, brain stem transmission time was relatively unaffected by sound pressure direction or acoustic frequency spectrum. These results were utilized in a comparison of brain stem evoked response parameters in normal and autistic children. Recently reported latency differences and differences in brain stem transmission time were not confirmed.

RELATIONS BETWEEN CONTINGENT NEGATIVE VARIATION
AND BEHAVIOR UNDER PSYCHOACTIVE DRUGS IN MAN

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We have tested the reliability of the contingent negative variation (CNV) as an index for behavioral evaluation under psychoactive drugs in fifteen voluntary subjects. Statistical analysis was performed of the relevant relationships between electrophysiological parameters [amplitudes of the pre-imperative negativity (N) and of the post-imperative positivity (P)] and reaction time (RT).

Five conditions were studied: (1) Standard (S1-L2), paired stimulations of a conditioning sound (S1) and an imperative light (L2) with motor response; (2) Disagreeable (S1-E2, with an electric shock as an imperative stimulus; (3) Uncertainty (S1-?) with a randomized suppression of the imperative stimulus and a separate averaging of complete and incomplete sequences; (4) Positive Reinforcement (S1-L2-RT) by indicating RT; (5) Negative Reinforcement (S1-L2-E3) with an electric shock when RT was too long.

In five patients CNVs were studied during three sessions before and after administration of chlorpromazine (CP) 10 mg, morphine (Mo) 1 cg or placebo (Pl) (intravenous injection).

In ten patients CNV were recorded during three sessions, after oral administration of a benzodiazepine (lorazepam - Lo; diazepam - Di) or placebo (Pl). Placebo effect was seen only after intravenous injection (low increase of amplitude and greater dispersion of RT). CP and Mo modified the CNV in all the situations. There were increased N and P amplitudes of CNV and increased RT with CP. Under Mo, RT was unchanged while CNV decreased, then disappeared with reversal after 45 minutes. CNV and RT changes after Di and Lo were selective, only seen in reinforcing conditions (increased N, decreased P waves of CNV and increased RT as compared to the standard conditions).

These data suggest that there is no linear relation between CNV amplitudes and RT. Further CNV studies for the evaluation of psychoactive drugs must be referred to individual psychometric tests.

EVOKED POTENTIAL ABNORMALITY AND DISABILITY
IN BRAIN DAMAGED PATIENTS: A REPLICATION STUDY
AND PRELIMINARY FINDINGS IN RELATION TO OUTCOME

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Evoked potentials were obtained in a clinical setting from brain damaged patients (with head injury and other types of CNS damage) using auditory, visual and somatosensory stimuli. Brain stem and cortical responses were judged for degree of evoked potential abnormality (EPA).

Correlations between EPAs and initial disability ratings for brain damaged patients (N=92) were positive and significant. Findings in this study replicate those previously reported. In addition, the EPA rating procedure was tested and found to have significant inter-rater reliabilities. It is concluded that EPA ratings can be used to aid in the assessment of the clinical condition and degree of overall brain dysfunction in brain damaged patients at all levels of consciousness.

In a selected sample of head injury patients (N=30) a significant relationship was found between extremes of EPA score and eventual outcomes. These are preliminary findings and require replication

Evoked potentials representing cortical activity were found to be the most informative in reflecting overall brain functional status. The major components of these EPs have been shown by others to be related to basic cognitive functions such as habituation and attention. It is felt that the degree to which these higher level brain functions are preserved indicate a patient's potential for positive outcome.

The need for further refinement in EP testing procedures and in the method of utilizing combined EP and other pertinent clinical data to improve prediction of outcome is indicated by cases with paradoxical outcomes.

ELECTROCORTICAL MANIFESTATIONS OF COMPLEMENTARY
HEMISPHERIC SPECIALIZATION IN AN EXPECTANCY TASK

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Subjects were tested in a cued reaction time (RT) task wherein warning stimuli (WS) were briefly presented as five letter words or dot patterns randomly intermixed across trials. After 2 sec, an imperative stimulus (IS) of the same category as the WS appeared, and the subjects pressed a key with the left or right hand. The right key was pressed if the IS word was a synonym of the WS word or if the IS dot pattern was the same as the WS pattern, and the left was pressed for antonyms or different patterns. It was predicted that CNVs would be larger over the left than right hemisphere on word trials and vice-versa on pattern trials in accordance with speculations concerning hemispheric specialization. The CNV was lateralized as expected, most prominently on pattern trials. In addition, a negative transient potential and a late negative post-imperative slow wave were similarly lateralized. P300 waves were very large, and largest to the IS when the IS differed from the WS, but P300 exhibited no lateralization. The results indicate that it is possible to induce CNV differences in the hemispheres without employing overt verbalizations by subjects in response to the IS, so avoiding associated artifacts and enhancing the clinical usefulness of CNV asymmetry. The lateralized anticipation may be construed as a differential attentional set. Lateralization of the negative component of the response to the IS is compatible with such an interpretation as that component appears to reflect attention to stimulus parameters that define an input channel. Attentional channels, then, may be defined in terms of specialized hemispheric/cognitive functions. The substrate of cognitive set onto which a stimulus impinges may strongly influence the extent to which EPs evoked by the stimulus are lateralized. Thus, the failure to assess "prior state" in EP asymmetry studies may account for much of the confusion in that literature.

THE EFFECTS OF OPTICAL BLUR AND GRATING ADAPTATION
ON AMPLITUDE AND PHASE OF EVOKED POTENTIALS

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Optical image degradation and preadaptation of the eye to high contrast gratings (Blakemore and Campbell, 1969) both may reduce the visibility of low contrast gratings. We showed how these effects are correlated to reductions of EP amplitude. Significant temporal EP phase shifts have been observed only as a result of grating adaptation.

We used the EP recording technique of Campbell and Maffei (1970). The EP amplitude measured as a function of spatial frequency reveals significant effects of blur only at frequencies above 5 Hz. The EP phase linearly increases with log spatial frequency and closely correlates with the latency of neuromagnetic responses (Williamson et al., 1978) and Breitmeyer's (1975) psychophysical reaction time data. The phase, however, is not significantly affected by blurring the retinal image. Briefly, the accuracy of meridional EP refractometry is better than ± 0.5 D only if EP amplitudes are considered and the eye is stimulated at higher spatial frequencies (Rentschler and Spinelli, 1978).

Grating preadaptation of the eye causes a loss of EP amplitude and induces EP phase shifts as well. These effects show interocular transfer, as it is known, from psychophysical studies. We observed a decrease in latency when preadapting the ipsilateral eye and an increase in latency when adapting the contralateral eye. No subjective counterpart of such effect is known. The interocular transfer of grating adaptation might be used as an EP technique for testing binocular function in children.

OPERANT EVOKED POTENTIAL CONDITIONING IN ANIMAL AND MAN

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E.R.A., C.N.R.S. no. 07.0624 (Neurophysiologie de la Vision).

With the operant conditioning technique, we trained ninety human subjects to modify their visual EP configuration. For half of them, training induced stable modifications restricted only to the reinforced wave. These modifications disappeared with extinction. Such results led us to some fundamental questions: (i) Is it possible to rule out any peripheral mechanism, i.e., are we dealing with true CNS activity conditioning? (ii) Which pathways and/or structures can account for these modifications? Some answers came from animal studies. We were able to train curarized rats to change their visual cortical EP waveform. Modifications exhibited the same characteristics as for man; they were strictly restricted to the wave submitted to reinforcement, susceptible to polarity reversal and disappeared with extinction. According to Graybiel (The Neurosciences, Third Study Program, 1974, M.I.T. Press), we recorded the responses of some structures along the "lemniscal line" and the "lemniscal adjunct" system. We could not find at the LGN level the waveform modifications evoked at the trained cortical site. We also recorded the EP activity of the NPT (nucleus posterior thalami) where Disterhoft and Stuart (J. Neurophysiol., 1976, 39, 266) found the earliest neural responses to a conditioning paradigm. This nucleus exhibited the same waveform alterations as those emitted in the cortical trained site. Moreover, successful training of the visual evoked activity of NPT itself showed us that this center must play an important role in operant conditioning of neural events. But further investigations are necessary to determine whether the observed modifications of NPT activity have a real sub-cortical origin or if they are a simple reflection of cortical activity.

VISUAL EVOKED POTENTIALS DURING STIMULUS
DISCRIMINATION LEARNING

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During stimulus discrimination, learning the relevancy of stimulus attributes changes with increasing practice. At the beginning all the stimulus attributes will be seen as equally important, and they will be processed with an equal amount of attention. At later stages of the acquisition phase, the subject can concentrate solely on those attributes which have been shown to be relevant and ignore all the others. The present experiment was designed to determine whether these hypothesized changes in attentional set are reflected in amplitude changes of the vertex evoked potential.

Method: Two-element visual stimuli, each composed of a circle (varying in size) and a triangle (varying in shape), were paired with different responses. In one group of subjects only the dimension circle-size was relevant for the correct stimulus-response identification, while triangle-shape was irrelevant. In another group the opposite held. The two attributes of each stimulus were presented separately in time. Thus, evoked potentials picked up from Cz to A2 could be averaged separately for different stages of the acquisition phase and separately for the relevant and the irrelevant stimulus attributes. The experiment was run with a total of thirty-one subjects. Results: While percentage of correct stimulus-response associations increased linearly over blocks, systematic amplitude changes could be observed in two positive peaks (P160 and P330) of the AEPs. First, the amplitudes of both components decreased continuously with increasing learning progress. Second, with increasing practice the amplitudes to the irrelevant attributes became significantly smaller than those to the relevant attributes. Third, the point at which the amplitudes to relevant and irrelevant attributes diverged was different for the two components. It was earlier for the P330 and later for the P160. The fact that the amplitudes of the two positive peaks showed different trends with increasing practice suggests that they reflect functionally distinct processes of attentional set.

THE UTILIZATION OF EVOKED POTENTIALS IN PSYCHOPHARMACOLOGY
AND PHARMACOPSYCHIATRY

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Quantitative evaluation of drug-induced alterations of latencies and amplitudes of human evoked potentials (EP) of normal volunteers resulted in characteristic "pharmaco-EP profiles" for the major classes of psychotropic drugs. Anxiolytics produce EP profiles characterized by a latency increase in early peaks and a decrease in late peaks of the secondary components, as well as by an attenuation of the amplitudes in general. In contrast, neuroleptics induce a latency increase in all peaks which, together with an amplitude attenuation, is especially prominent in the late portion of the EPs. This was also observed in chronic schizophrenic patients. Interestingly, therapy responsive patients showed different changes than therapy resistant ones: while the former revealed a marked latency increase during neuroleptic therapy, the latter showed only minor alterations or even changes in the opposite direction. There were no significant inter-group differences. Neuroleptic treatment of psychotic children resulted in an increase of both latencies and amplitudes, which was correlated with clinical improvement and represented a ("normalization") shift towards the EP patterns observed in age and sex matched normal children. Stimulatory drugs produced in normals a latency decrease in the early as well as in the late part of the EP. Contrarily, in hyperkinetic children an increase in latency was observed with d-amphetamine (as was observed with the neuroleptic thioridazine), which seems to be the neurophysiological correlate of the well known "paradoxical" clinical response of these children patients to amphetamine. Therapy responsive children showed more latency increase and amplitude augmentation than therapy resistant ones. Some pre-treatment VEP values were correlated with clinical outcome. EP profiles of antidepressants depend largely on their chemical structures: while MAO-inhibitors induce alterations similar to those of stimulants, tricyclic antidepressants produce a latency decrease in early and a latency increase in late EP components. The amplitudes are generally attenuated. The neotropic drug Hydergine was found to increase SEP amplitudes. Based on these pharmaco-EP profiles, new compounds were successfully classified: while halazepan and clorazepate and the anti-androgene cypoterone acetate induced changes typical for anxiolytics, the androgene mesterolone produced alterations similar to thymoleptic drugs.

DISCRIMINATE FUNCTION MODELS OF ERP DATA IN HYPERACTIVE CHILDREN

James H. Satterfield, M.D.

Data will be presented that illustrate several problems in using event related potential data to discriminate between hyperactive and normal children (ages 6 to 12 years). Since some ERP amplitudes change twofold in this age range and since these changes differ between normal and hyperactive children (interaction with age), careful attention to this interaction is a necessary first step. Spuriously high (95%) correct classification can occur if too many variables are used to construct the model. With a reduction of the number of variables to only eight, a discriminate function developed on the same set of cases (as in the problem with 95 variables) correctly classified 90% of the training set and 76% of an unknown set.

The percent of cases correctly classified is dependent upon the chance way in which the split is carried out for the simulated replication. This was demonstrated by pooling all hyperactive and all normal cases and then randomly selecting one-half of each of two groups. Half of the cases in each group were combined and used as a training set, with the remaining cases used as an unknown set. All cases were then repooled and the above procedure repeated twenty times. Twenty discriminate functions were developed from the twenty training sets thus selected, and those functions were tested against twenty unknown sets. The mean correct classification for the twenty sets of training cases was 82% (SD = 7.8). The mean correct classification for the twenty unknown sets was 81% (SD = 8).

Major conclusions: (1) The success of the classification of twenty random split halves found here suggests potential usefulness of discriminate function models of ERP data as an aid in diagnosis. (2) The percent of cases correctly classified in split half replication studies using discriminate function models varies considerably, depending upon the particular (chance) split utilized. (3) The mean performance on a series of split half simulated replications is a better estimate of the ability of such models to separate groups than is any individual simulated replication. (4) When looking for ERP abnormalities in children, group interactions with age must be considered.

AUDITORY EVOKED POTENTIALS AS PROBES OF LATERALIZED
INFORMATION PROCESSING IN ADULTS AND INFANTS

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Recently, Shucard, Shucard and Thomas (1977) reported a study in which cerebral specialization of function was assessed using auditory evoked potentials (AEPs) to pairs of task-irrelevant tones to probe activated brain sites involved in ongoing information processing. Other investigations have been conducted in our laboratory to elaborate on the original findings and to study the phenomenon in infants.

The original findings have been replicated in a new adult sample. In exploring the relationship between monopolar and bipolar placements, a negative relationship was found between AEP peak amplitudes obtained from temporal scalp placements referenced to Cz (T4-Cz, T3-Cz) versus temporal placements referenced to linked ears. For example, when T3-Cz showed a higher amplitude response relative to T4-Cz during verbal information processing, and T3-linked ears showed a lower amplitude response relative to T4-linked ears during the same task. These findings indicate that reliable predictions can be made about evoked activity at the temporal sites whether a Cz or linked ears reference is used.

Using our "two-tone probe technique" to study the development of cerebral specialization of function in awake, three-month old infants, we found significant sex dependent differences in left versus right hemisphere AEP amplitudes. While listening to complex auditory stimuli such as language and music, seven out of eight male infants showed a higher amplitude right hemisphere AEP as compared to the left for N300, whereas, seven out of eight females showed a higher left hemisphere response relative to the right for the same peak. Similar results were obtained as well for P200 and P400 AEP peak amplitudes. No such relationships were found when the tones were presented alone without the verbal and musical stimuli. These findings support previously reported behavioral studies of developmental sex differences in analytical and spatial information processing which may be related to the influence of sex hormones on the developing brain.

The auditory probe technique might prove clinically useful for early detection of disabilities which are thought to be related to disturbances in cerebral organization. (Supported in part by NICHD Grant HD 11747.)

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AUDITORY EVOKED POTENTIALS INDICATE ATTENTIVE
DYSFUNCTIONS IN HYPERKINETIC ADOLESCENTS

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From the files of a children's clinic, thirteen 12 to 13 year-old boys were selected who had childhood diagnoses for hyperkinesia (HK), IQ above 84 and no neurological or psychiatric disorders. The controls (CG) were fifteen age-matched normal boys. The selective attention (SA) task consisted of dichotic series of 180 tone pips (50 msec, 75db SPL) of 800 Hz to one, and 1500 Hz to the other ear, with random interstimulus intervals (mean of 793 msec). Approximately 20 signals (840 Hz or 1560 Hz) were randomly interspersed. Subjects were instructed to count signals to one ear (Attend). Four series were given, counterbalanced for the attended ear and frequency. Averaged EPs (vertex to mastoid) to the pips were computed to the attend (AT) and non-attend (NA) channels. N100 amplitudes (baseline to peak) showed no significant group differences for NA. N100 was significantly higher under AT than NA conditions for the CG, but not for the HK group. Mean amplitude enhancements were 43% for CG and 13% for HK. P300 to the attend signals was found for every boy, with means of 9.51 μ V for the CG and 6.74 μ V for the HK (insignificant difference). Correlations between P300 and N100 AT were .48 for CG and .20 for HK. P300 to nonsignal pips were unremarkable.

Two behavioral tasks were button-press responses to the signals for the SA and for a 10 minute vigilance task which consisted of bin-aural 1500 Hz pips (40 per min) with 64 signals of 1560 Hz. On both tasks the HK made significantly fewer correct responses and more errors of commission than the CG. Also, on the vigilance task, reaction times to correct responses were significantly longer and more variable for the HK group. For SA, correlations between correct responses and N100 AT enhancements were -.03 for CG (mean 81% correct) and .57 for HK (mean 42% correct). Dichotic listening to sixty pairs of real syllables (pa, da, etc.) resulted in mean correct responses of 63.7% for CG and 54.7% for HK, and insignificant right-ear advantages for each group (means of 7.73 and 6.77). For lateral preferences, the incidence of consistent right hand-eye preferences was 67% for CG and 23% for HK, while crossed preferences were, respectively, 20% and 77%.

These findings demonstrate the applicability of the SA paradigm for EP measures of attentive dysfunctions in HK children. Their deficient N100 enhancements reflect deficits in selective attention, while their normal P300 waves would indicate adequate detection of the relevant signals. (Supported by a grant from The Grant Foundation.)

DIMINISHED CNV REBOUND AND PERSEVERATIVE ATTENTION SET
IN OLDER SUBJECTS

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There are two CNV effects of potential value in clinical work - the CNV distraction effect which is exaggerated in schizophrenics and psychosurgery patients, and the CNV rebound effect which is absent in psychosurgery patients. The present study assessed these effects in two age groups. Twenty-one young subjects (ages 18-28) and thirty-one healthy older subjects (ages 56-85) were tested in two CNV paradigms. The first was a control condition where a light flash (first stimulus of S1) was followed in 1.5 secs by a continuous tone (second stimulus or S2) which was terminated by an operant key press (control trials). The second condition involved a random presentation of two types of trials: no-letters trials which were identical to control trials, and letters trials which were similar to control trials, except that three successive visual letters were presented within the S1-S2 interval for recall after the key press to S2. A control condition preceded and followed the mixed condition. Both young and older subjects showed a slowing of reaction time ($p < .001$) and a reduction in amplitude of CNV ($p < .01$) recorded at Fz, Cz and Pz in letters trials compared to control trials (CNV distraction effect). For the young group, amplitude of CNV reached supranormal elevations (above control values) ($p < .01$) in the no-letters trials at each recording site (CNV rebound effect). The older group showed CNV rebound effects at Cz and Pz ($p < .01$) but not at Fz. CNV rebound appears to reflect a switching of attention process between the divided-attention set of attending to letters and tone in letters trials and the unified attention set of attending to tone in no-letters trials. Consequently, the absence of normal CNV rebound in frontal brain areas of the elderly may indicate some type of loss of resiliency of brain functioning that becomes expressed in a perseverative attention set.

LATE COMPONENTS OF THE AUDITORY EVOKED RESPONSE IN SCHIZOPHRENICS

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This study was carried out using ten normal controls and twenty patients selected from forty-five recorded patients (ten acute and ten chronic schizophrenics). All were matched for age, sex and educational level, and patient groups were matched for medication dosage level. They were exposed to a 15 min sequence of frequent/infrequent auditory stimuli (85% of 60 dB - 320 Hz vs 15% of 60 dB - 1000 Hz with interstimulus intensity (ISI) : 5 sec), and were told to count infrequent stimuli. All the controls counted correctly, but only ten of the twenty patients were able to execute the task. Averaged evoked potentials (AEP) were recorded for the frequent and infrequent stimuli from Cz and Pz and one ocular site.

The most interesting findings were the following:

1. Nosological effect: The late positive component (LPC) amplitude (peak of maximum positivity between 300-500 msec) was larger for controls than for schizophrenics, but there was no difference between acute and chronic schizophrenics. Since some patients did not perform the task we could not distinguish the effect of the psychotic process from that of the subject option.
- 2) Behavioral effect: As could be expected, the most striking differences were seen between the LPC of controls and schizophrenics who counted poorly (Cz and Pz - $p < 0.001$). In this last group, there was no significant difference between the AEPs evoked by frequent and infrequent stimuli. This finding demonstrated that the attitude of the patient toward the experiment played a major role.

However, there were also differences between controls and schizophrenics who counted well. The latter displayed clear LPC but no significant difference between frequent and infrequent stimuli. These patient-control differences were seen in P3a and SW components, particularly in the development of N210 and the occurrence of an additional negative peak N3 (mean latency: 380 msec) which overlapped the early positivity process.

Thus, patients may have different electrophysiological potentials even when they perform a task as well as the normal subjects. These data raised the problem of whether we are faced with a different strategy or with a different brain reactivity.

HAAR TRANSFORMS OF EVENT-RELATED POTENTIALS:
TOWARD AN OPTIMAL RE-EXPRESSION OF THE DATA

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Linear transform methods, routinely used to reduce ongoing EEG data, have been applied sporadically to event related potentials as a way to re-express the data with fewer variables (i.e. to reduce dimensionality).

The most popular transforms with fixed basis function, Fourier and Walsh-Hadamard, are pure frequency representations that span the whole epoch and blur the information contained in the physiologically significant time sequence of ERP components. The Haar transform escapes this loss by using basis functions that occupy separate time windows. At each successive level (i.e., order) the windows become narrower (by one half).

A comparative study is presented that shows the efficiency of the transform in encoding visual ERP information. Discriminant analyses (stepwise) applied to both raw and transformed data demonstrated simultaneously an increase in discrimination performance and a reduction of dimensionality.

The Haar re-expression lies halfway between time and frequency analysis. It is sensitive both to local and global features of the signal with the high-order terms becoming progressively more local. The ability to capture local components is a major asset for ERP analysis. In addition, the Haar functions take the form of single "alterations", a waveform characteristic that mimics ERP components fairly well.

Finally, it seems that further improvements could be obtained if the constraints imposed by orthogonality and basis functions fixed in time were relaxed. Such a waveform directed data transformation is certainly realizable but still remains to be implemented and tested. It would bring the long sought after capability for automatic component separation.

DEVELOPMENTAL CHANGES IN ERP PRECEDING MOVEMENT:
RELATION TO VARIABILITY AND IQ

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Waveforms preceding right thumb flexion vary with development and mental retardation (Karrer et al., in press). We have replicated these waveforms in children, preadolescents and in normal and mentally retarded young adults. EEG during thumb flexion (button press) was recorded DC between Oz, Cz, C3, C4, Fz and linked ears. Activity occurring 920 msec pre-EMG to 320 msec post-EMG was classified by form using explicit criteria.

The frequency of waveforms at Cz confirmed developmental changes in their distribution. The retarded's distribution of waveforms was different from the normal's. Positive components at 600 and 150 msec prior to movement characterize the child's waveform. Young adults had typical negative-going waveforms. Retarded had uniphasic positive-going waveforms. Preadolescents exhibited all waveform types. We also confirm the relation of positivity to a measure of movement extraneous to the task (discarded eye movement artifact). In all children positivity at C4 is directly related to the amount of extraneous movement ($r = +.49$), and this is strongest in children showing the typical "child's" waveform ($r = +.85$). This relation resides at different leads depending on waveform in children, preadolescents and MR, but not in adults. Waveforms did not differ on number of trials averaged, trials excluded due to eye movements or in trial-to-trial variability, nor were they a function of background EEG. Variability for all waveforms increased over the epoch to a maximum at the response. Between groups there was a variability increase with decreasing age and mental retardation. However, within groups there was no relation of IQ to variability.

Children showing a waveform characteristic of the adult had higher IQ ($X=113$) than those showing the typical "child's" waveform ($X=101$) though there was no age difference. For "adult" waveforms, the less the positivity the greater the IQ for adults ($Fz:r = -.83$), children ($Fz,Cz:r = -.90, -.78$) and retarded ($Oz:r = -.79$ $p < .1$). This positivity that relates to IQ occurs between 600 msec and response depending on group and lead.

These data support the concept that different waveforms preceding movement occur as a function of age and mental status. The positivity that characterizes the waveform of the physically and mentally immune is functionally related to IQ and to the inhibition of movement irrelevant to performance.

Supported by NICHD grant HD08265.

EVOKED POTENTIALS IN THE DIFFERENTIAL DIAGNOSIS OF SENSORY AND
NEUROLOGIC IMPAIRMENT IN CHILDREN

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A combination test consisting of cortical auditory evoked potentials (EPs), brain stem auditory EPs and visual EPs to flash has been found to be very useful in assisting in the differential diagnosis of sensory and neurologic impairment in children. Data on clinical referrals for such testing over a one year period at C.H.N.M.C. were analyzed. Among children who had normal brain stem EP thresholds, those referred with a suspicion of hearing loss had cortical auditory EP amplitudes approximately 50% lower than children with no auditory symptoms. No differences in BEP latencies were found between the two groups.

EP latency did, however, differentiate between children with and without a history of neurologic deficits. Children with known neurologic deficits had longer brain stem and cortical auditory EP latencies than children with no neurologic symptoms whether or not they presented with symptoms of an auditory deficit.

An evoked potential index (EPI) was devised to quantify the "abnormality" of an EP. The EPI was found to differentiate normal children from those suffering from the effects of severe malnourishment (marasmus). Although the EPIs of the children improved during the course of treatment, they were still deviant at the time of discharge and at follow-up tests a year or more later. These abnormalities may reflect a long lasting effect of malnutrition on brain function (Barnet et al., *Science*, 1978, 201, 450-452).

In addition to the above findings, six case studies taken from patients seen in this laboratory in the past six months are discussed. The patients presented with symptoms of auditory and visual deficits. EP test results helped confirm a variety of final diagnoses including brain stem encephalopathy, hemianopsia, cortical blindness, peripheral hearing loss and "cortical deafness". The patients ranged in age from six months to five years. The utility of EPs in these differential diagnoses was dependent upon careful individualized design of the test parameters and procedures for each patient. Benefits of EP testing were maximized when the test was designed to allow the patient to serve as his own control. Analysis of EP results was often assisted by comparing BEPs and AEPs, results from left ear or eye and those from the right or results from two test sessions.

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